GUIDING PRINCIPLES OF SAFETY AS A BASIS FOR DEVELOPMENT OF A PHARMACEUTICAL SAFETY CULTURE

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Abstract

Despite the best effort of industry and regulatory authorities, the trust of society in the process of medicine development and communication of pharmaceutical risk has ebbed away. In response the US government has called for a culture of compliance while the EU regulators talk of a 'culture of scientific excellence'. However, one of the fundamental problems hindering progress to rebuilding trust based on a pharmaceutical safety culture is the lack of agreement and transparency between all stakeholders as to what is meant by a 'Safety of Medicines'. For that reason, we propose 'Guiding Principles of Safety for Pharmaceuticals' are developed analogous to the way that Chemical Safety has been tackled. A logical starting point would be to examine the Principles outlined by the US Institute of Medicine although we acknowledge that these Principles require further extensive debate and definition. Nevertheless, the Principles should take centre stage in the reform of pharmaceutical development required to restore society's trust.

Introduction: What are the wider issues that impact on Pharmaceutical Safety?

The development of medicines is in the doldrums. An inexorable upward spiral in the costs of drug development has been accompanied by a collapse in confidence and trust in the industry-regulatory authority axis [1].

In addition, professionals working in the pharmaceutical sector are faced with evermore guidances, increasing complexity of rules and regulations, and enhanced legal, financial, and regulatory scrutiny. Persistent pressures to improve the efficiency of the development process are further coupled with fierce competition particularly with generic manufacturers.

The U.S. Institute of Medicine assessment of the current system for evaluating and ensuring drug safety in order to make recommendations to improve risk assessment, surveillance, and the safe use of marketed drugs, has served to introduce more uncertainty [2].

All of this is set against a background of several financial scandals undermining confidence in corporate America, with implications worldwide since pharmaceutical companies are largely global. In response to these financial scandals, a recent Chairman of the Securities and Exchange Commission, which oversees the financial services industry in the United States, wrote:

"What's really needed is not necessarily more laws, but rather the full engagement of business leaders in an effort to advance an underlying spirit of reform. These reforms must inculcate a company-wide mindset to do the right thing, and must become part of the DNA of the corporation" [3].

This concept of doing "the right thing" is central to the confidence society requires for the pharmaceutical sector, a collective term for the pharmaceutical industry (and all its dependents) and regulatory authorities. Not only does this sector have to ensure access of medicines to those who need them – and at a fair price – but the industry-authority axis must also act safely. Thus doing "the right thing" must be acknowledged as the core goal for the sector.

Reliance on regulations alone will not work

Many inside and outside the pharmaceutical research enterprise have reasonably assumed that with extensive legislation and regulations in place in the three ICH regions, supplemented with further guidance from groups such as CIOMS, product safety and society's confidence in the decisions are assured. However, it appears that reliance on the regulatory process for safety and the way compliance is applied are simply not enough. The sector urgently needs to understand what the various stakeholders in society desire from 'Safety' as both acceptable and appropriate and, in turn, how this should be applied to pharmaceutical development. This means appreciating that, for instance, safety of pharmaceuticals is much more than just case report management. As pointed out by Waller and Evans, collecting adverse drug reactions is assessing **harm** not necessarily **safety** [4]. In addition, for the pharmaceutical industry, there is a pressing need to understand **that safety equates with compliance** in the sense of 'doing what you say you will do.' rather than just simply following SOPs based on regulations

Guiding Safety Principles for Medicines to underpin a Culture of Safety

Although there are common standards for protection of patients during research as laid out in the Declaration of Helsinki (there is global agreement on, at least, the 1996 version), there is no agreed framework, based on a set of guiding principles, with all the other relevant stakeholders about what meant by 'Safety of Medicines'. This is all the more surprising given the scientific evidence available now about the nature of compliance and risk, why people make mistakes and thus how organisations can act safely [5].

Fundamentally, what is lacking is a set of Principles to guide understanding of safety and risk in development and marketing of medicines to which all stakeholders have agreed. Such Principles would address all aspects of development activities, including manufacturing, pharmaceutical organisation, communicating and managing risk and all those clinical processes which directly involving patients.

The Guiding Principles released by PhRMA about Direct-to-Consumer advertising may be a step in the right direction in the way they indicate industry recognition that voluntary standards are required to retain trust [6]. This is juxtaposed by the recent comments suggesting the need for further changes in the development and marketing practices of the pharmaceutical industry [7]. In a different venue, as part of a consensus statement from an international conference (about generic HIV products), before the assembly could agree about what constituted a safe HIV drug they proposed "establishing international principles that need to be taken into account when considering the safety and quality of these drugs " [8].

However, what constitutes a 'Principle' is itself open to debate and currently may vary from organisation to organisation. But, neither semantics nor excessive literalism must entrap us. For instance, although the Luxembourg Declaration about Patient Safety was not specifically directed at safety of medicines, this Declaration implicitly covered medicines as a form of technology when stating the need "to encourage the development of internal standards for the safety and performance of medical technology" [9].

In short, Guiding Principles can contribute to the development of standards on which a pharmaceutical safety culture might be based consistent with the aim of the Declaration and the recommendation of the seminal book published by Institute of Medicine in 1999 10].

Concept of Guiding Principles as a basis for safety is not new in Society

It is not a new idea to develop a safety culture based on Principles (which are then regulated using a risk-based approach) to not only include but also go beyond a culture based on rules. Much of what constitutes safety culture and our understanding of risk and compliance has arisen from applying Health & Safety legislation. Although we are extrapolating from industrial accidents to compliance and safety in pharmaceutical development, the pharmaceutical sector can learn a lot from the experience of other organisations and the struggles they have had with implanting a safety culture. In particular it is worth studying closely those industries, which must comply and produce a safe product to prevent rapidly visible and fatal consequences.

There is now persuasive evidence from safety science suggesting that compliance failure and defective safety behaviour, such as might occur for benefit-risk decision-making, arises from basic faults in organisational structure, safety climate and processes rather than individual mistakes or misconduct. Thus the pharmaceutical sector should look at the extensive evidence that has now accumulated about how to create a safety culture. Looking more closely at how other industries have approached safety by making substantial changes in the way they operate to help retain society's confidence brings the nuclear energy sector to mind.

Following the Chernobyl accident, the International Nuclear Safety Advisory Group (INSAG) was the first to introduce the term safety culture [11]. As well as this INSAG paper on safety culture, the most useful reference for appreciating transferable information to the research enterprise is the Advisory Committee on the Safety of Nuclear Installations (ACSNI) - Organising for Safety [12]. In response to society's concern about the risks posed by chemicals, the OECD drafted Guiding Principles for Chemical Accident Prevention, Preparedness and Response. These Guiding Principles set out general

guidance, applicable worldwide, to prevent chemical accidents at facilities where there are hazardous substances and to mitigate adverse consequences of accidents that nevertheless occur through emergency preparedness, land-use planning and emergency response [13].

The important point to apply within the pharmaceutical sector is that these Guiding Principles for managing risk from chemicals addressed **all** stakeholders, defined as any individual, group or organisation that is involved with, interested in, or potentially affected by chemical accident prevention, preparedness or response – including, among others, management and other employees of hazardous installations; public authorities at all levels including local authorities and response personnel; communities/the public and non-governmental organisations).

Thus, there is a substantial challenge – one being the consultation process for developing global Guiding Safety Principles for medicines. However, to illustrate where to start, a set of internationally applicable Guiding Principles are under development for food safety based on what was previously drafted by FDA in collaboration with other stakeholders [14], [15].

Safety culture is the desired outcome

We should not forget that the purpose of the Guiding Principles is to provide framework of common understanding for creation of a safety culture. Then we can implement processes within a system for the protection of patients (pharmacovigilance). However, various definitions have been used for safety culture. The Confederation of British Industry perhaps most succinctly expresses the concept of culture as "the way we do things round here" [16]. Hence, culture is indeed reflected in the way a company behaves towards the people it serves. Managers already understand the importance of culture in attracting and retaining best employees, how reputation depends on managing integrity and how long-term support from investors is linked to accountability and transparency. This is reflected in the fuller definition of safety culture suggested by the Health and Safety Commission in the UK:

> "The safety culture of an organisation is the product of the individual and group values, attitudes, competencies and patterns of behaviour that determine the commitment to, and the style and proficiency of, an organisation's health and safety programmes. Organisations with a positive safety culture are characterised by communications founded on mutual trust, by shared perceptions of the importance of safety, and by confidence in the efficacy of preventative measures." [17].

From various studies it is clear that certain factors appear to characterise organisations with a positive safety culture [10] [18]. These factors include:

- The importance of leadership and the commitment of the chief executive;
- The executive safety role of line management;
- The active involvement and commitment of all employees;
- Effective communications based on commonly understood and agreed goals;
- Good organisational learning and responsiveness to change;
- Manifest attention and insight into product safety and health implications for patients; and,
- A questioning attitude and a rigorous and prudent approach by all individuals.

The ACSNI report contains a prompt-list of indicators of positive safety culture intended to assist organisations in reviewing their own culture [12]. Improving safety culture implies a long term, systematic and systemic process, based on an initial assessment of the existing safety culture, determining priorities for change, the actions necessary to effect the change and then going on to review progress before repeating the process indefinitely. In short: continuous improvement is through change management with the focus on developing and maintaining a culture of safety.

Who might "own" the Guiding Principles of Safety for a pharmaceutical organisation?

From the infrastructural vantage on a culture of safety, companies might consider establishing a Corporate Safety Office within the overall corporate compliance structure, which could then include the qualified persons for pharmacovigilance, and GMP among others. Such an Office could oversee implementation of the Principles, safety culture and advise how these should be monitored in a way

meaningful to the entire organization. Is it so far fetched to believe that in the future someone like the qualified person in pharmacovigilance might be the owner of the Guiding Safety Principles for a particular company?

Safety culture based on Guiding Principles could be central to rebuilding trust.

The pharmaceutical sector, and in particular the industry, needs to be willing to learn from other organisations that have been successful in making complex systems work more safely. This is required to reassure society products are of acceptable standards of quality and safety. These standards should be based on internationally agreed Guiding Principles of Safety applied to existing scientific and public health criteria.

Moreover, developing safety culture to surround and apply these Principles is strongly related to the current thinking about Quality systems. A safety culture and a quality system are intimately related; indeed, they need to be integrated in helping an organisation cope with errors, compliance aberrations, and manage risk. In addition, there is now substantial evidence to show that errors are often the result of faulty processes within a system rather than a single individual's failings. Thus 'being safe' is an approach to working together with a commitment to continuous improvement and elimination of waste. Finally, like Quality (and human research protections, another part of a systemic culture of safety), safety is not a capital-added expense – it is an organisational attitude to be learned. Errors are important for individual learning, that is, people learn from errors. For organisations, the best way to manage and control safety is through learning from experience.

Significant cultural change in the leadership, professional participation and daily work of organisations involved in pharmaceutical development is inevitable. Just as how pharmaceutical organisations should act safely to regain society's trust should be at the forefront of senior executives' thinking and actions, how product and patient safety should be integrated into corporate social responsibility and governance should be equally high on the decision-making agenda.

Expressed in another way, to rebuild trust, both the industry and regulatory authorities need to reassure more clearly patients, shareholders, and other stakeholders that operations are conducted in a responsible and sustainable way based on mutually agreed Guiding Safety Principles. Making apparent – and transparent – a culture of safety is the means to do so.

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