

Risk rationale

Pharma needs a culture of proactive pharmacovigilance and risk minimisation

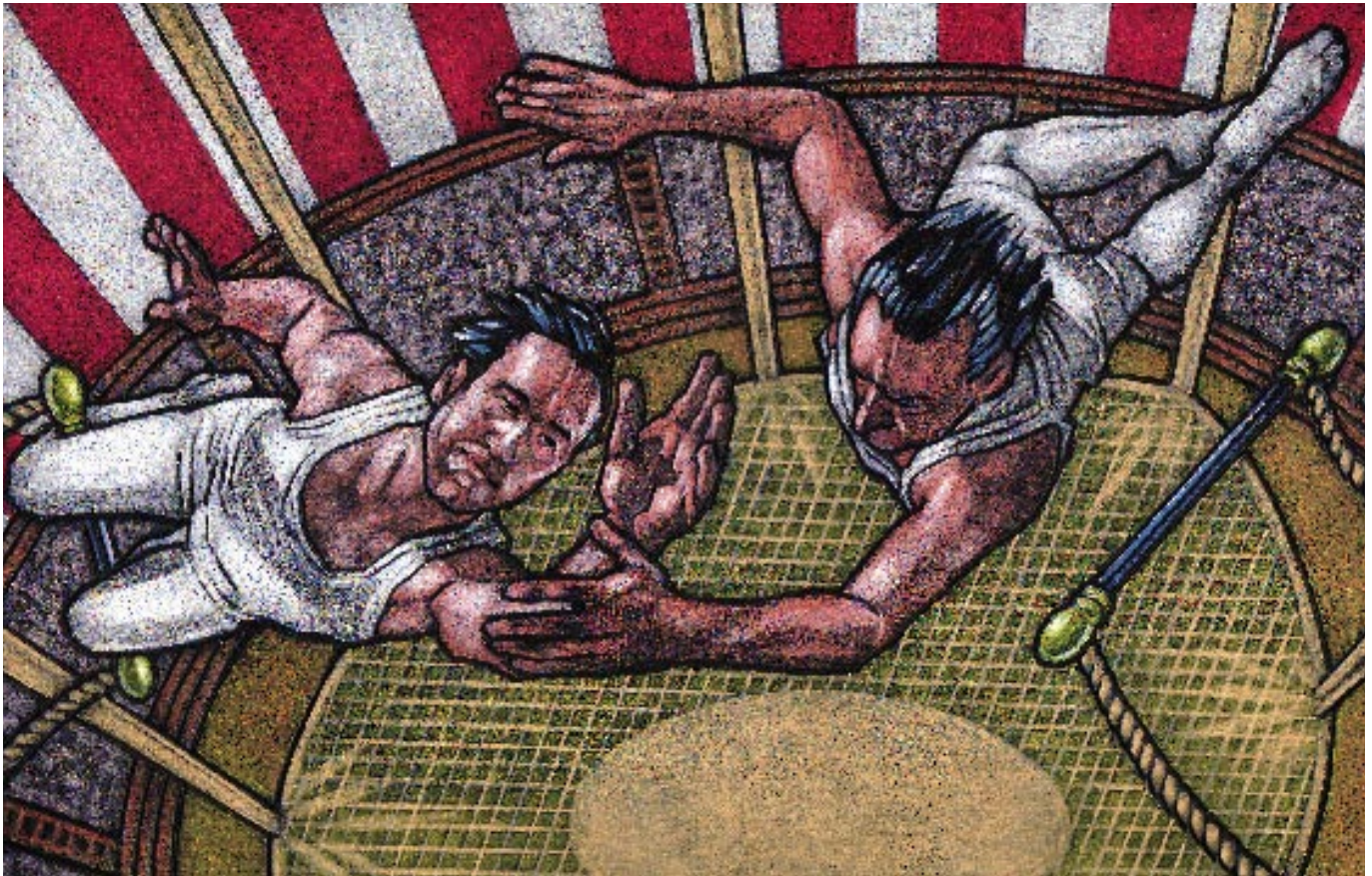


Illustration by David Jukes

Pharma firms and government bodies have placed increasing emphasis on managing and communicating risk. This is driven by many factors, notably increasing public anxiety about safety and recent high-profile product restrictions and withdrawals – Merck’s Vioxx, Elan and Biogen Idec’s Tysabri and Novartis’s Zelnorm.

There is a raft of new regulations and guidelines, but regulatory and post-marketing authorisation monitoring systems are sometimes suboptimal.

Many risk management interventions were designed and implemented in reaction to new safety information, mainly in an attempt to avoid product withdrawal. There is now a desire for a continuous improvement culture with proactive pharmacovigilance and risk minimisation methods (see figure 1).

Pharma is subject to stringent regulation throughout the life of the product. To obtain marketing approval, firms have to provide evidence that the product is both efficacious and safe, including preclinical and clinical data, as well as evidence of good manufacturing practices. Yet, at approval, safety data is still limited.

Patient numbers mean that most clinical trials cannot detect rare adverse events or anticipate ‘real world’ usage and associated safety issues. As well as greater patient numbers, post-approval usage differs with age, ethnicity, co-medication and time of exposure. Multiple outcomes also mean that statistical problems may be encountered in clinical trials. Regulators weigh up potential benefits against potential risks, but not all potential risks have been identified at the time of approval.

DEVELOPING AN RMP

To minimise the risk of adverse effects after approval, there are regulatory frameworks for statutory post-marketing risk management plans (RMPs), and in the EU a risk management strategy (EU-RMP) is required. There have been changes in the requirements of the application for authorisation of products for human use (EC Regulation No 726/2004 and Directive 2001/83/EC). Article 8 of the Directive states: “A detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce”.

This is the legal basis for the guideline and the context in which an EU-RMP should be set. An EU-RMP may be needed in the pre- or post-authorisation phases. In particular, an EU-RMP is required before the approval of any product containing a new active substance, any biosimilar product or any generic medication where the innovator product had safety concerns.

An EU-RMP must also be produced upon changes in marketing authorisation, or on request from a competent authority. It is strongly recommended that discussions with the competent authorities on the need for, and content of, an EU-RMP should take place in advance of any submission. An EU-RMP has four elements: risk detection, risk assessment, risk minimisation and risk communication. It comprises two parts:

Part I:

- safety specification
- pharmacovigilance plan

Part II:

- evaluation of the need for risk minimisation activities
- risk minimisation plan (if there is a need for additional, ie, non-routine, risk minimisation activities).

It should describe methods to assess the effectiveness of the risk minimisation interventions. This is complex because:

- the EU-RMP is obligatory, making comparison between the frequency and impact of adverse events with or without EU-RMP impossible
- surveillance of patients post-approval differs from that during clinical trials because of numbers, procedures and clinical settings
- in practice it is difficult to measure the impact of the EU-RMP on adverse event frequency and severity.

The US, the Food and Drug Administration has not made risk minimisation action plans mandatory but does strongly advise it at the time of filing, particularly for a new chemical entity or biologic.

COMMUNICATIONS

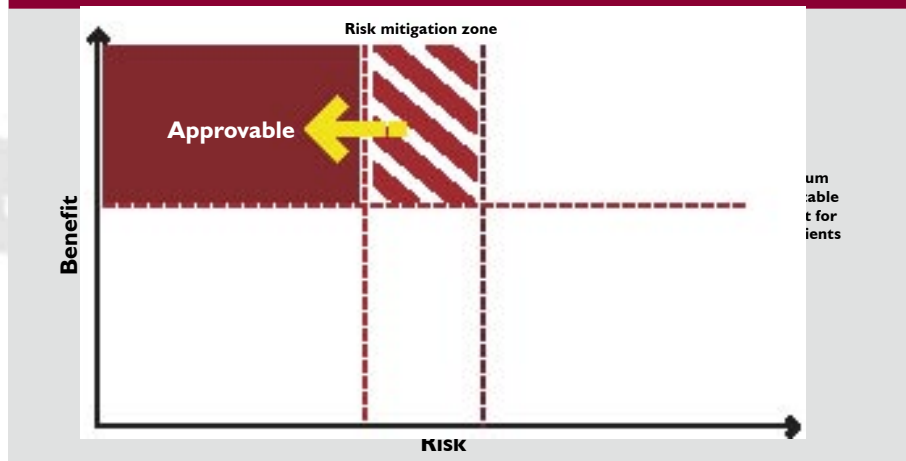
Most RMPs depend on effective risk communications. It is valuable to systematically identify, characterise and, therefore, anticipate how a real world treatment pathway may affect the intrinsic risks, such as hazard identification and failure mode and effects analysis (FMEA). This can form the basis of a rationale for suitable risk minimisation strategies (see figure 2).

Many risk minimisation strategies have been ineffective as communications have:

- targeted a narrow range of people rather than all relevant stakeholders (eg, only doctors rather than healthcare teams, patients, carers etc)
- failed to tailor messages to audiences
- used inadequate vehicles to deliver messages (eg, use of passive communications alone such as 'Dear Dr' letters).

Successful risk minimisation programmes take a systematic approach, incorporating a comprehensive communication plan and materials, with interventions designed to modify behaviours. They include a range of feedback and evaluation mechanisms to measure their effectiveness, allowing for improvement and modification.

FIGURE 2: RISK MINIMISATION – THE PURPOSE



Pharmaceutical firms should include an integrated communications and training strategy to help staff understand the rationale and assist in the implementation of the risk minimisation programme.

ROOM TO IMPROVE

Much progress has been made but some areas still need to be improved:

- **More focused safety specifications:** Safety specifications often lack focus and are based heavily on, or identical to, the integrated safety summary available at the time of filing. Best practice is a targeted summary of key pre-clinical and clinical data raising areas of concern, which can be linked to identified risks, potential risks and missing information.
- **Consideration of enhanced pharmacovigilance measures:** Routine pharmacovigilance may be sufficient for some RMPs, but often additional approaches such as labelling, post-launch commitments and expedited reporting, together with phase IV study commitments are needed.
- **Improved evaluation of the need for risk minimisation:** There is often little or no explicit assessment of risk minimisation need and no rationale offered is for the risk minimisation tools proposed.

- **More practical and integrated development of risk communication tools:** In common with medical education and marketing activities, many risk communication tools aim to educate or to support decisions. A multidisciplinary approach to development is essential.
- **Earlier and more effective cross-functional planning of programme roll out:** Often, the programme roll-out and communication tools have sub-optimal multidisciplinary planning and communications, and/or insufficient or absent global-to-local affiliate training. The main purpose of an RMP falls within the patient safety and regulatory domains, but if RMP tools can assist prescribers and patients in the optimum use of the drug, this benefits the industry, the product and corporate brand image.
- **Better post-launch evaluation and ongoing improvement:** Often, not enough thought is given to the post-launch evaluation and distribution of risk minimisation tools/communications, as well as the mechanism to incorporate feedback to continuously improve the tools/communications.

A survey by Pope Woodhead published in *Drug Safety* suggests senior managers in drug development and marketing view risk management as an opportunity to improve the pharma industry's image with regulators, prescribers and patients and believe that the quality of risk minimisation programmes may differentiate companies and brands.

A successful RMP requires close working relationships between all key functions – pharmacovigilance, marketing, regulatory affairs and drug safety. This underpins the importance of effective, integrated risk communications.

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