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Tolerability of risk approach and the management of pharmaceutical risks

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> "…this approach reflects the view that things are not usually either 'safe' or 'not safe', but that they can be made to be 'safe enough'."

Public trust in policy makers, industry officials and opinion shapers is declining in Western societies, a trend highlighted by opinion polls, surveys and research [1–4,101], which leads to political crisis, substantial economic losses and the introduction of controversial risk-regulation practices, such as the precautionary principle [5–8]. Is the post-Vioxx® pharmaceutical model of risk regulation immune to such developments?

The tolerability of risk (ToR) framework constitutes a model of consensus regulation successfully used by the UK regulator of health and safety to help make decisions concerning risk [9]. It has been recently considered to offer a promising heuristic for improving the quality of public health decisions [10]. How much could the pharmaceutical sector learn from the ToR approach?

What is ToR & where does it come from?

Since 1842, the UK regulators have introduced the term 'best practice', holding the belief that regulation should be as flexible as possible. Regulation should follow a 'reasonably practical' or 'best practice' rule [11]. For the last 50 years, safety has been appreciated in the UK according to the following principles: on the one hand it is the responsibility of the regulated to ensure that risks are maintained as low as reasonably achievable or as low as reasonably practicable (ALARP). A constant trend of regulation and case law requires, on the other hand, a comparison of the risk and the sacrifices (money, time and trouble) involved in taking measures to avert risk. If the sacrifice appears to be disproportionate when compared with the benefit from reducing the risk, then the requirement has been met and implementation of additional measures is not required [102].

Therefore, this approach reflects the view that things are not usually either 'safe' or 'not safe', but that they can be made to be 'safe enough' [12], and that several parameters should be included in the decision-making process. Instead of emphasising 'the initial integrity of safety of critical hardware or substances,' the UK approach focuses on 'risk assessment combined with exposure limits that can be measured and therefore successfully controlled and in use and properly enforced' [13]. This constitutes a 'gross disproportion' safety philosophy that, to be socially acceptable and effective, requires clear procedural rules [14]. In 1972, the Robens Committee, evaluating the UK safety system, came to the conclusion that procedural clarity was missing and that there was a need to define criteria for the balancing of the respective interests of the state and other actors [15]. Following the Health and Safety Act based on the findings of the Robens Committee, the ALARP principle became the UK standard. The Health and Safety at Work Act (HSWA, 1974) and others. organized duties to establish and maintain safe working conditions and practices in the workplace.

By the 1980s, the Health and Safety Executive (HSE), the regulator appointed under HSWA, had developed considerable competence in the practice of risk assessment. As a result of this and

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the increasing evidence base provided by extensive research programs, the judgemental nature of ALARP decisions in most industrial situations posed few problems that could not be resolved [12]. However, in high-hazard industries, such as nuclear or chemical sectors, the nature of the risks, the potential effects on the public and the high levels of expenditure associated with risk-reduction options led to the idea that a unifying philosophy and procedure should be developed to deal with risk reduction. This question came to the fore in the report by Sir Frank Layfield on the planning inquiry for the controversial Sizewell B nuclear power station [16,17]. Sir Frank proposed that HSE should 'formulate and publish guidelines on the tolerable levels of individual and societal risk to workers and the public from nuclear power stations' [18]. In response, the HSE developed the ToR framework [19,20], a model subsequently generalized for wider application to all industrial risks [21].

ToR in use today: the HSE model

ToR can be described as a useful framework 'for reaching decisions whether the risks of an activity or process are unacceptable, tolerable, or broadly acceptable and its application in practice. In this context 'tolerable' does not mean 'acceptable'. It refers instead to a willingness by society as a whole to live with a risk so as to secure certain benefits in confidence that the risk is one that is worth taking and that it is being properly controlled' [21].

> "...tolerable does not mean 'acceptable'. It refers instead to a willingness by society as a whole to live with a risk so as to secure certain benefits..."

ToR is presented visually as a triangle, some may say 'carrot' (FIGURE 2, *EXPERT REV. CLIN. PHARMACOL.* 1[2], 241–250 [2008]): the triangle represents increasing levels of 'risk' for a particular hazardous activity, as we move from the bottom of the triangle towards the top. The triangle can be divided into three broad regions:

- The zone at the top represents an unacceptable region. For practical purposes, a particular risk falling into that region is regarded as unacceptable;
- The zone at the bottom represents a broadly acceptable region. Risks falling into the region are generally regarded as insignificant and adequately controlled;
- The zone between the unacceptable and the broadly acceptable region is the tolerable region. Risks in that region are typical of the risks from activities that people are prepared to tolerate in order to secure benefits. Risks must be maintained ALARP.

The three regions are delineated by tolerability criteria, that is × number of deaths per annum. A key point is that these numbers are built in a way that takes into account probabilistic estimates regarding a risk, but also society's views. Such an approach will typically imply a mix of statistical estimates concerning individual risks and surveys of public perception. In theory, if not in practice [14], boundaries between tolerability regions should be different for each activity. For example, nuclear risks and road safety will have substantially different tolerability criteria attached to them. With regards to the inclusion of societal concerns, the HSE has focused only on concerns arising out of society's aversion to large-scale accidents [22].

Tolerability of risk has been considered 'very flexible and can react more or less instantly to new technical information or perceptions of risk' [23]. The ToR framework has been used only for technical issues rather than big political dilemmas. It has no legally binding status. It is, therefore, a guiding heuristic and each duty holder gives content to the approach, taking account of the specificities of scientific and human situations.

How can ToR be used in the pharmaceutical sector?

Could a ToR-like model be developed in the pharmaceutical area? A number of key issues should be addressed before attempting to import the ToR heuristic into the pharmaceutical area, including:

- Pharmaceutical regulatory culture
- The inclusion of stakeholders' views
- The nature of pharmaceutical risks

Railways safety constitutes an area where the efficiency of the ToR model was challenged in the late 1990s as a result of highly publicized accidents, such as the Ladbroke Grove accident. The controversy was amplified by concerns that the privatization of the railway system led to 'a highly fragmented industry with train operations both separated from the ownership as well as the management of the infrastructure and exposed to competition and with infrastructure maintenance often contracted out to third parties' [24]. ToR works because, unlike railway safety, all of the interest groups involved in health and safety have an over-riding common objective. Employers, trade unions and governments share an interest in maintaining a reasonable balance between risk taking and protection. As a result, risk-reduction measures are generally consensual [11,25]; pharmaceutical regulatory culture is often defined as 'corporatist' or 'consensual' [26,27]. Industry and the government clearly share the common objective of delivering better health. So, in principle, ToR could work.

> "ToR works because ... all of the interest groups involved in health and safety have an over-riding common objective."

Compared with the model, however, the views of third parties are not significantly involved in the regulatory process [28]. A review of recent pharmaceutical 'media hypes', including the measles, mumps and rubella vaccine scare in the UK, the

hepatitis B controversy in France [29] and the Vioxx scandal in the USA and Europe [30], shows that only weak or inconsistent attention is paid to public perception. Several methods could help to include public views into pharmaceutical risk decisions. One approach, which has been used by regulators, is 'political' and relies on various mechanisms of information, consultation and participation [31]. Such mechanisms work best in areas where society does not trust the regulator's allocation of risks and benefits [4]. For this reason, most routine decisions regarding risk reduction may require another approach. The analysis of public perceptions uncovered by cognitive sciences may offer a workable alternative in safety areas where people do not feel concerned. Cognitive sciences have focussed on expert preferences and determinants of perceptions, including familiarity, control, catastrophic potential, equity and level of knowledge [32–36,103].

ToR has been particularly successful in relation to acute risks, such as accidents, particularly those arising in nuclear and on- and off-shore major hazards. The model struggles when risks are difficult to characterize [21,22]. The model also requires a clear view of the costs involved by individual events. Compared with occupational risks, drug-related risks can be pervasive or their materialization can be delayed substantially. Despite regulatory safeguards requesting 'thorough' studies, drug trials and pharmacovigilance, health risks are difficult to assess and sometimes fuzzy or misleading [37]. Instruments, such as biomarkers for example, are not designed to provide a clear picture of the statistical occurrence of risks [10,38] and their ability to inform cost–benefit assessment is limited [29].

Expert commentary

Adapting the ToR model would require taking better account of societal preferences to improve risk characterization and to cost risks and benefits more affectively. The task will be ambitious but the return in terms of improved decisions and social support for the decisions could be high.

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