An effective quality risk management (QRM) process provides a key mechanism for the proactive identification and control of potential issues that may arise during product development and subsequent commercialisation. In this context, risk is defined as the combination of the probability of occurrence of harm (or unwanted outcome) and the severity of that harm (or unwanted outcome). Scientific approaches are used to estimate the likelihood of any given context, risk is defined as the combination of the probability of occurrence of harm (or unwanted outcome) and the severity of that harm (or unwanted outcome). Scientific approaches are used to estimate the likelihood of any given context.

During the 1960s, manufacturers were required to demonstrate the safety of food and colour additives. The ‘Delaney Clause’ prohibited the use of any additives known to cause cancer in man or in animals. The FDA was required by law to apply a ‘zero-risk tolerance’ approach to food additives. By the early 1970s, it became clear that this approach was untenable and would lead to a large scale ban of animal feed products. There was also a much clearer understanding that exposure to small quantities of food additives does not materially increase the risk of contracting cancer, i.e. there is an acceptable risk / benefit ratio, which prompts the question: Is zero risk attainable or even desirable?

Over the last 50 years, the UK government’s general approach towards the responsibility of the regulatory agencies towards risk management has been to maintain risks “as low as reasonably practicable” (ALARP). There is then a balance between the risks encountered versus the expended effort (time, cost and effort). If the expended effort is disproportionate to the perceived benefits accruing from reduction of risk then the necessary ‘duty of care’ has been fulfilled and additional measures are not required. Hence risk resolution should be viewed from a perspective of ‘safe enough’ or acceptable rather than from an absolute perspective of safe or not safe. This led to the Toilerability of Risk (ToR) approach, which subdivides risk into unacceptable, tolerable or broadly acceptable; where tolerable does not equate to acceptable, but instead reflects 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’. That is, where an acceptable risk / benefit balance has been attained and the cumulative benefit to the patient outweighs the inherent risk.

Therefore, clinical studies for oncology products typically involve patients whose disease state is progressive, often fatal. Therefore, as the clinical outcomes are so poor, the ‘tolerable risk’ can be higher. For example, in oncology products, a case can be made for managing mutagenic impurities according to the guidelines for standard impurities (ICH Q3A/Q3B), rather than the much more restrictive guideline for mutagenic impurities (ICH M7).

Delaney was in agreement with this pragmatic approach, reflecting that, “Should the issue of genotoxic impurity limits in pharmaceuticals be resolved from the perspective of historical precedent (the zero risk tolerance mindset), or from a more carefully considered cancer-risk avoidance and risk management viewpoint that weighs the new regulatory burdens against the benefits conferred by pharmaceutical products to patients?”

Delaney contended that the ICH M7 guidance often ignores the reality that pharmaceutical syntheses frequently needs to use highly reactive intermediates (DNA reactive, i.e. mutagenic). He estimated that about a quarter of all reactive intermediates used in synthesis would likely be mutagenic. By focusing on the need for avoidance (i.e. risk averse), the guidance sets an inappropriate expectation for chemists to expend greater efforts to utilise synthetic options that are often considerably less efficient, employing ‘non-green’ chemistry, without materially improving patient safety. Therefore, the degree of risk that can be tolerated is predicated on prevailing circumstances, the proximity of that risk to the end user, especially if additional controls can be introduced after the process that is being assessed and prior to the product being provided to the patient.

In conclusion, it seems apparent that a consensus across industry and regulators on risk assessment / mitigation strategies is required. Otherwise, different perceptions of risk will prevail and risk will continue to be in the ‘eyes of the beholder’.

References