Impurities can be defined as those by-products of synthesis of the drug substance or by-products of manufacture / storage of the drug substance or drug product. They include organic, inorganic, residual solvent and mutagenic impurities (MIs).

Organic impurities comprise starting materials, intermediates and degradation products. Inorganic impurities comprise reagents, ligands, residual metals (including catalysts), etc. Residual solvent impurities can be found in both drug substance or drug products, but are typically controlled in the former. Mutagenic impurities are DNA reactive and are highly toxic.

Typically, there are no therapeutic benefits to be derived from impurities; the exception being closely related impurities in proteins, peptides, or semi-synthetic products, eg, oligonucleotides, beta-lactams, etc, where these analogues often retain biological efficacy and are often controlled as families or classes of impurities. It has been argued that avoidance – especially for highly toxic impurities, ie, MIs, is justified and is a logical extension of any control strategy. However, many experts have indicated that as “reactive intermediates are essential to synthesise complex, multifunctional APIs [Active Pharmaceutical Ingredients], the avoidance of risk of MIs is not tenable, as it is practically impossible to avoid entirely all reactive intermediates.”

Therefore, all impurities should be removed or controlled, where possible, to meet product specifications, good manufacturing practices (GMP), or other quality- or safety-based criteria. Drug products should contain no higher levels of residual impurities than can be supported by safety data or process capability. For commercial drug substance and drug products these safety-based control strategies are enshrined in the International Conference on Harmonization (ICH) guidelines covering impurities in drug substance (ICH Q3A(R2)) and drug product (ICH Q3B(R2)), residual solvents (ICH Q3C(R5)), residual elemental impurities (ICH Q3D) and residual MIs (ICH M7(R1)).

In marked contrast to the control of MIs, there is limited guidance available for the appropriate control of non-mutagenic impurities during clinical development. The European Medicines Agency (EMA) indicates that limits should be set based on batch results in non-clinical and clinical batches; however, if there are limited numbers of batches this requirement can be constraining. As such, regulators often default to ICH control strategies, even though EMA guidance indicates that “compliance with ICH requirements is not required, if proper justification is provided”.

Notwithstanding this caveat, ICH limits are totally inappropriate for early phase development, where batch-based experience is, by definition, incomplete and restricted.

In an effort to provide both industry and regulators with scientific guidance on safe, allowable levels of non-mutagenic impurities (NMI), an industry consortium reassessed the supporting information from several key in vivo toxicology databases that support and underpin the ICH Q3A(R2) defined concept, “that a lifetime dose to 1mg/day of a NMI would not represent a safety concern to patients”. This 1mg/day value can be used as a universal qualification threshold for an NMI during any stage of clinical development. This analysis also proposes that modification of this 1mg/day dose using an established methodology; ie, Modified Haber’s Law (this approach is also enshrined in the ICH M7(R1) guidance), can support 5mg/day or 0.7% (whichever is lower), as an acceptable limit for a NMI in a drug substance in early clinical studies (<6 months).

A similar analysis for drug product impurities demonstrated that a 5mg/day or 2.0% (whichever is lower) can be supported as an acceptable limit for an NMI in a drug product in early clinical studies (<6 months). Such safety-based limits should be beneficial in early development where by definition there is limited knowledge of impurities available and strategies to control them.

Listen to Dave Elder explain why he chose to write about non-mutagenic impurities in our exclusive podcast at www.europeanpharmaceuticalreview.com.