Most pharmaceutical facilities are multi-use, in that they are used to manufacture a variety of different chemical entities and drug products, with the exception that certain potent or sensitising classes of drug product are exempt. This latter group is required to be manufactured separately, in segregated or dedicated ‘self-contained facilities’. Therefore, cleaning of manufacturing equipment and facilities is a requirement of the existing cGMP regulations in order to prevent cross-contamination. Cleaning is a classical ‘risk reduction measure’ and limits for cleaning validation programmes are routinely developed”. Unfortunately, there has been limited consensus in this area, that is, visually clean equipment: ≤ 10 ppm of the next product and ≤ 10,000th of the daily dose limits have all been proposed”. Importantly, these different approaches do not take account of the available underpinning safety data.

Recently, the European Medicines Agency decided that a more scientific approach was warranted for both risk identification and to support any risk reduction strategies for different classes of pharmaceutical substances. As such, they introduced a new cleaning guidance*. These health-based cleaning limits align with recent thinking on impurities such as residual solvents (ICH Q3C(R5)), residual elemental impurities (ICH Q3D) and residual mutagenic impurities (ICH M7), thus, the presence of such contaminants (or impurities) should be controlled according to the severity of the risk posed. This, in turn, is related to those levels that can be considered safe for all exposed populations. The guideline* therefore recommends safety-based exposure limits for these contaminants via the determination of a safe threshold value. Determining such a value – for example, permitted daily exposure (PDE) or threshold of toxicological concern (TTC) values – requires making a risk assessment of all available pharmacological and toxicological information, using both non-clinical and clinical data.

However, there is a key distinction between impurities and contaminants. The former are typically related substances formed as bi-products of the synthesis or degradation products produced during manufacture and/or on storage of the active pharmaceutical ingredient/drug product. Although impurities offer no benefit to the patient, as integral bi-products of the manufacture of the product they warrant safety-based limits according, in extremis, to lifetime exposure. This is enshrined in ICH Q3A(R2), Q3B(R2), Q3C(R5), Q3D and M7. In contrast, contaminants would not be expected to be present in each and every batch, nor at the same levels in every batch, that is, they are a ‘one-off event’. Indeed, when multi-batch campaigns or continuous manufacturing are employed, any equipment carryover will be greatest within the first batch of any campaign or at the beginning of any continuous manufacturing processes.

This raises the intriguing question: if contamination is a ‘one-off event’ and extremely unlikely to affect every batch to the same level, why are lifetime-based safety limits, such as PDEs or TTCs, employed? Indeed, ICH M7* recognised that these safety limits were based on a modification of Haber’s Law which states that a patient’s exposure is a combination of the absolute amount of the impurity multiplied by the total time of exposure to the impurity, up to a maximum of 70 years. They therefore introduced the concept of less than lifetime (LTL) exposure which states that if the time of exposure to the impurity is decreased then the absolute amount of the impurity can be increased, i.e., the exposure multiple is the same. Therefore, for the first time in man a limit of 120µg/day can be used rather than the default TTC of 1.5µg/day, which is based on a 70 years lifetime exposure. It would, therefore, seem logical that the health-based cleaning limits should also use a modified PDE based on the fact that contamination is a one-off event, rather than the standard PDE, which is based on lifetime exposure.

In conclusion, the provision within the EMA document of guidance for allowable limits of residual contaminants is to be welcomed. The EMA guideline indicates that “deviation from the main approach highlighted in this guideline to derive such safe threshold levels could be accepted if adequately justified”. It is to be hoped that modifications based on a LTL PDE could be adopted in the future.

References
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