STANDARD ISSUE

Dr Albrecht Poth, Dr Knoell Consult, examines biological evaluation and the challenges and consequences for the medical device industry

CHEMICAL REACTION: ***The changes of ISO standards will impact medical device manufacturers by putting more emphasis on chemical characterisations, says Dr Albrecht Poth***

The important standards for biological evaluation and risk analysis of medical devices are explained in three parts. ISO 10993-1 provides the framework and describes the general principles of the biological evaluation; ISO 10993-18 provides information on the qualitative and quantitative characteristics and finally ISO 10993-17 gives guidance on the derivation of the allowable limits for the leachable components of the medical devices. All the three major standards are going to be revised substantially

For ISO 10993-1 "Evaluation and testing within a risk management process" the final draft international standard (F-DIS) has been published in January 2018. The revision will include a change in the flow-chart describing the systematic approach of the biological evaluation including as an initial step the chemical characterisation. As a consequence Annex A 1 "Evaluation tests for consideration" of ISO 10993-1 has been revised by adding a new column including chemical characterisation as a test parameter. It will further include additional test parameters for certain device categories and additional toxicological endpoints for evaluation based on the US-FDA modified matrix as outlined in the US-FDA guidance document "ISO International Standard ISO 10993, Biological evaluation of medical devices Part 1: Evaluation and Testing" (2016). By including additional requirements it was discussed that chemical characterisation is the only mandatory testing requirement and all other toxicological endpoints will be evaluated on a case-by-case basis within a toxicological risk assessment.

A major revision of ISO 10993-17 on allowable limits for leachable substances is in works. The experts of TC 194 are discussing risk assessment approaches to use the concept of Threshold of Toxicological Concern (TTC), a concept which is already established and accepted for genotoxic pharmaceutic impurities. If it can be shown that an impurity is below the TTC, then it is assumed that the level of the chemical substance is of no significant risk and no further evaluation is required with regard to that impurity. The TTC allows definition of threshold values for substances below which there is insufficient material available to cause a toxicological hazard and thus no further evaluation is required. The concept may also be applied more generally to unidentified contaminants. The inclusion of TTC in Part 17 would be a significant advance which will allow avoidance of unnecessary animal testing if chemical characterisation can demonstrate that leachables are below the TTC. This concept is planned to be implemented in the revisions of ISO 10993-17.

A major revision will also be made to ISO 10993-18 "Chemical characterization of materials" including the technical and scientific experience made during the last 10 years since its publication in 2005. A second Committee Draft (CD) was published in January 2018, including the choice of extraction types (exaggerated versus simulated-use extraction) and a better definition of the experimental requirements for investigating extractables and leachables. It will further include a description on the stepwise chemical characterisation process and the revisions needed to the associated flowchart. The revision will include approaches for setting analytical evaluation thresholds (AETs), recognizing that this will have to be developed in alignment with thresholds of toxicological concern (TTCs).

It can be foreseen, that the proposed step-wise chemical characterisation will be of more complexity especially for high risk devices, including more complex chemical analytical methods for structure elucidation of unknown chemical substances released but also the evaluation of release kinetics of chemical compounds from medical devices.

Based on the proposed revisions it can be foreseen that in future the chemical characterisation will be a key parameter in the assessment of the biological evaluation of medical devices within a risk management system. Toxicological hazard and risk assessments will also be key aspects not only for the evaluation of extractables and leachables but also for the evaluation of raw materials and their impurities.

Overall, the changes and adaptations of the ISO standards will impact the biological evaluation strategies of manufacturers of medical devices by putting more emphasis on chemical characterisations and sound toxicological evaluations. Thus, the era of the 'tick-the-box of the flowchart' mentality for animal studies in the medical device business is to be replaced by systematic evaluation approaches taking into account the chemical composition of the devices.