Toxicological Risk Assessment of Medical Devices:

Upcoming changes in regulatory expectations and a new draft of ISO 10993-17
Introduction

Since the publishing of the FDA Guidance on the Use of ISO 10993-1 (2016), and ISO 10993-1:2018, there has been a greater emphasis on chemical characterization and toxicological risk assessment of medical devices within a risk management process. The purpose of conducting these evaluations is to better understand risks associated with medical device exposure, and to address these risks either with the risk assessment (if appropriate for the endpoint) or with biological testing. This approach allows for a better understanding of risks, and an informed selection of tests to address biological risks. It will also help to avoid unnecessary testing. With the recent increase in chemical characterization requirements, there has also been an increase in the conduct of toxicological risk assessments. Toxicological risk assessments are needed to interpret the chemical characterization data, and to identify potential risks to the patient.

There is a strong emphasis of ISO 10993-1 and FDA Guidance on the Use of ISO 10993-1 on toxicological risk assessments. However, currently there is a lack of published guidance on the conduct of toxicological risk assessments for medical devices. ISO 10993-17, which was last revised in 2002, describes the derivation of allowable limits of leachable substances in medical devices, and not toxicological risk assessment. ISO 10993-17 is now being revised substantially by the ISO TC194 working group (WG 11) and will soon become a new Committee Draft (CD). The proposed new title of ISO 10993-17 is “Toxicological Risk Assessment of Medical Device Constituents,” and the revised standard will expand from current guidance on establishing allowable limits of leachable substances, to conducting a toxicological risk assessment of medical device constituents. Topics to be addressed will include hazard identification, exposure assessment, dose-response assessment, and risk characterization. There will be emphasis on the use of expert judgment to determine whether the toxicological risks of exposure to extractable or leachable chemicals in medical devices are acceptable, what additional steps may be taken to mitigate risk, and when to recommend risk control.

Four Important Steps in a Toxicological Risk Assessment

A toxicological risk assessment is the act of determining the potential of a chemical/compound to elicit an adverse health effect based on a specified level of exposure. Conduct of a toxicological risk assessment includes four important steps: Hazard Identification, Dose-Response Assessment, Exposure Assessment, and Risk Characterization.

Hazard Assessment

Hazard identification is described as the processes used to evaluate the inherent property of a constituent to elicit/induce one or more adverse health effect(s), as well as the conditions (e.g., route, duration, frequency, sex, age) necessary for the constituent to elicit the adverse health effect(s). Hazard identification includes obtaining adverse health effect data most commonly, but not limited to, toxicity studies conducted in animals and reported in original reports, or secondary sources such as peer reviewed published papers, authoritative reports, databases, etc. The adequacy and quality of the data used to determine the Point of Departure (POD) should be justified. The POD may be a no-observed adverse effect level (NOAEL), a low-observed adverse effect level (LOAEL) or a benchmark dose (BMD). In the absence of relevant high quality toxicity data and POD, a threshold of toxicological concern (TTC) may be applied based on the technical specification ISO/TS 21726.

Dose-Response Assessment

The dose-response assessment includes selecting the lowest most clinically relevant POD (e.g. a NOAEL from a repeated dose toxicity study in animals), and applying the appropriate uncertainty factors to derive a tolerable intake (TI) in µg/kg/day, a threshold protective for human health. Uncertainties typically include extrapolation between animals and humans, variability between humans, route of exposure, duration of exposure, and data quality/gaps. In the absence of relevant toxicity data, a TTC can serve as the TI.
Exposure Assessment

Exposure assessment is the process for estimating the quantity of a constituent of toxicological concern that contacts (external dose) or enters (internal dose) the body. In most cases, the total amount of each chemical in an extraction study (following ISO 10993-18) is assumed to be released daily. The relevant patient population and total number of devices used daily should also be included in the worst case exposure dose (µg/kg/day). If toxicological risks associated with particular chemicals are identified during risk characterization, additional refinement of chemical characterization (e.g. a simulated use extraction study) may be used to better estimate more clinically relevant exposure dose.

Risk Characterization

To determine if the risk of exposure to an extractable or leachable chemical is acceptable, a toxicologist will calculate a margin of safety (MOS). This is the comparison of the TI or TTC to the maximum exposure dose. The MOS of 1 has historically been interpreted as the bright-line of risk. MOS values above 1 are considered not likely to result in health related adverse outcomes for the endpoints evaluated (e.g. systemic toxicity, genotoxicity, carcinogenicity).

In the revised ISO 10993-17, the MOS is considered a tool, and not a bright-line of safety, and the draft guidance calls for MOS near 1 to have additional scrutiny. There are several reasons that this bright-line may need to be re-evaluated, as there are inherent uncertainties within the chemical characterization that can be a source of concern for the toxicological risk assessment. Chemical characterization is a semi-quantitative analysis, which may underestimate the amounts of the extractable and leachable chemicals coming from a device. Additionally, the identification of a particular constituent may be only tentative or poorly defined, creating uncertainty when the toxicologist is evaluating that chemical in the risk assessment. Another major uncertainty that lies within the toxicological risk assessment is that many of the studies used to determine a POD are from experimental data generated from animals, not humans. This leads to the use of additional uncertainty factors, which may not always be accurate between species. All of these can create a level of doubt that the MOS could be underestimated and a potential risk being overlooked.

WuXi AppTec has a large team of highly trained toxicologists that produce hundreds of toxicological risk assessments each year. Our risk assessments follow worst-case exposure dose estimations (daily exposure to total amount of each chemical), 100% bioavailability of each constituent, the use of appropriate uncertainty factors, and expert judgment to evaluate the risks associated with MOS values near 1. Chemical characterization studies often lead to a likely overestimation of exposure due to exaggerated solvents, temperatures and other extraction parameters, and expert judgment is needed to determine what additional steps should be taken to accept, mitigate, or control identified risks. WuXi AppTec’s team of toxicologists are able to apply their expert judgment to critically assess the potential risk presented by a device in holistic manner by combining the chemical characterization, biocompatibility data, and guidance from regulatory standards to evaluate safety and biocompatibility.

To find out how your business can use the testing knowledge base and industry experience of WuXi Medical Device Testing, please complete the contact us form at http://medicaldevice.wuxiapptec.com/contact-us/ and a representative will contact you.

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