LABORATORY TESTING DIVISION
MEDICAL DEVICE

White Paper

Unknowns are Unacceptable

Extractables/Leachables Program: Risk-based Approach to Complete Chemical Characterization and Toxicological Risk Assessment in Medical Devices

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The U.S. Food & Drug Administration (FDA) offers guidance for many industries, including those developing medical devices that come into direct or indirect contact with the human body. Specifically, there is the June 2016 FDA Guidance referred to as *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process."* The upcoming release of ISO 10993 Part 1, *"Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"* further complements the June 2016 FDA Guidance document.

Risk-based Approach to Clinical Device Safety Testing

The FDA is among the regulatory agencies adopting a risk-based approach to preclinical device safety testing. The risk-based approach comprises three main components: materials characterization, toxicological risk assessment and biocompatibility testing. These are the essential components for a complete biological evaluation.

The 2016 FDA Guidance states that a risk assessment should be conducted on the final finished device. It emphasizes that chemical characterization should be considered to identify the risks associated with medical device materials and include residual chemicals associated with "the processing of the materials, the manufacturing methods (including the sterilization process), and any residuals from manufacturing aids used during the process."

Components of Chemical Characterization

ISO 10993 part 1 provides further emphasis on chemical characterization and risk assessment for biological endpoints that generates an overall biological safety evaluation. Chemical characterization, also referred to as materials characterization, should be designed with the nature and duration of clinical exposure in mind. In addition, chemical characterization often involves an exhaustive or exaggerated extractables study and sometimes also involves a leachables study.

Extractables Studies

Extractables study designs challenge devices under more extreme conditions to maximize the extraction of chemicals from the devices and provide information for estimating potential hazards. For permanent implants and some prolonged devices, exhaustive extractions may be the appropriate method to maximize extractable chemicals that could be released from implants during long-term implantations.

Exhaustive extraction studies involve extracting devices in solvents with ranges of polarity and repeating the extractions until the amount of extractable material in subsequent extractions is less than 10 percent by gravimetric analysis of that detected in the initial extractions.

The intent of extractables studies is to determine the cumulative amounts of each chemical that could extract from devices over time. Exaggerated extractions may be the appropriate method to maximize extractable chemicals that could be released from limited and prolonged duration devices. Exaggerated extractions also use aggressive solvents and elevated temperatures to yield extractions. However, the studies may not necessarily involve complete or "exhausted" extractions.

Leachables Studies

Leachables study designs may be conducted to evaluate the potential for chemicals to extract or leach from devices under simulated-use conditions. These studies may be done in a solvent that simulates the environment of clinical use. For example, a mixed-polarity solvent may be used to simulate blood, a low-pH solvent may be used to simulate a gastric environment, and a drug itself may provide the appropriate matrix to determine device leachables in a combination product.

The intent of a leachables study is to mitigate risks that may be present in an extractables study that was performed. It can also provide information about exposure over time, using multiple time points, such as a nitinol (nickel) leaching study or provide information on the impact of a drug on the device in a combination (drug/device) product.

Study Processes and Challenges

In a typical extractables or leachables study, an extract is analyzed by several analytical methods, which may include gas chromatography-mass spectrometry (GC-MS; volatile to semi-volatile compounds), liquid chromatography-mass spectrometry (LC-MS; semi-volatile to non-volatile compounds), inductively coupled plasma mass spectrometry (ICP-MS; elemental materials), and headspace-gas chromatography mass spectrometry (HS-GC-MS; volatile compounds and residual solvents).

Although commercially available libraries to help identify chemicals in extracts exist, the LC-MS method does not have a commercially available library. Without a chemical library, the responsibility of identifying chemicals and building the library falls to the organization's analytical chemistry staff. This process of chemical identification is laborious and requires investment in key personnel and training. Establishing, building and refining an

internal database would alleviate some of the burden of identification. However, the process would involve a significant commitment of time, resources and expertise, as well as substantial investment in highly sensitive and accurate equipment.

Risk-assessment Approach Best Practices

FDA and ISO 10993 standards emphasize complete chemical characterization for identifying all of the chemical constituents in products. They also serve as the basis for toxicological risk assessments of the final finished devices. ISO 10993-17:2002 establishment of allowable limits for leachable standards outlines this risk-assessment approach. The risk assessment provides an analysis of risk that an adverse health effect could result from exposure to chemicals and elements in the device during intended clinical use. Important features of risk assessment are identification of potential chemical/elemental hazards (typically generated from extractables/leachables testing) and exposure (from understanding of the intended use of the device). The chemistry data, with complete chemical characterization, and the test article's indication of use, duration of contact and target population are necessary to conduct an effective risk assessment. Risk assessments should be used to guide which biological tests are required to mitigate the identified risks.

In the Event of Chemistry Report Unknowns

A chemistry report may indicate an unknown or unidentified chemical at an estimated concentration. To support a risk assessment, the amounts of each chemical should be reported as µg/device, and the analytical evaluation threshold (AET) should have been low enough to justify the reporting limit. Alternative reporting of µg/mL or µg/cm^2 requires a conversion to report as concentration per device, and it should be determined if the reporting limits were sufficiently low to support an acceptable risk for exposure to chemicals (µg/device) for the appropriate patient population. Lower reporting limits may be needed for multiple devices used clinically, and for pediatric or neonatal patients. Unknown or unidentified compounds are problematic in risk assessments.

Significant levels of unknown compounds are indicative of incomplete chemical characterization and, in a risk assessment, it must be assumed that these chemicals are potentially toxic, and conservatively treated as potentially mutagenic or carcinogenic to provide protection. For some devices, even unknown chemicals present at levels as low as 1.5 µg/device may result in an unfavorable risk assessment.

An unfavorable risk assessment may be costly for manufacturers due to uncertain product risks and delays in obtaining regulatory approval. In a well-conducted chemical characterization study and chemical risk assessment, if risks associated with specific chemicals are identified, they may be mitigated with additional chemistry testing and/or appropriate biological testing. With unknown chemicals, biological testing is not an option for mitigating risk, since the endpoints to be further evaluated are unknown.

Avoiding the Unknowns

Risk-averse organizations understand the importance of vendor selection for pre-clinical device safety testing. As medical device companies push the bounds of technology and begin to introduce unique and novel devices, it is imperative that the contract research organization you choose provides expertise and guidance on the evolving regulatory market. This commitment shows in the investments the research organization has made in its equipment and staff.

WuXi AppTec, located in St. Paul, Minnesota, has a state-of-the-art analytical chemistry laboratory, along with experienced scientists, chemists and toxicologists. Our chemistry experts understand that unknowns are not acceptable. After all, the success of your chemical risk assessment directly relates to the efforts our chemists make to identify and quantitate each chemical so that the toxicological assessment accurately reflects device-specific risks.

WuXi AppTec's investment in scientific experts and technology ensures the biological evaluation strategies and testing you require meet the latest regulatory standards. Our technical and regulatory experts serve as active participants and hold leadership positions within international regulatory standards committees. This allows us to anticipate regulatory changes. It is why we invest ahead of the final guidance into the programs required for global regulatory submissions. We anticipate regulatory requirements ahead of the published standards and guidances, and track regulatory trends. We guide our clients' test plans based on our industry knowledge, regulatory collaboration and the extensive number of products we have assisted through product clearance.

For more information about partnering with WuXi AppTec to avoid the unknowns in your project:

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