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The more you know, the more you save: a smart approach to chemical characterization

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Abstract

Medical Devices are often constructed of several materials and components, each with its own chemical and physical characteristics. To face their increasing complexity, standard committees and regulatory bodies had to focus on a more complete biological evaluation within a risk management process encompassing a thoughtful chemical characterization. Indeed, the upcoming revision of ISO 10993-1 and the recent FDA guidance on the application of ISO 10993-1 identify the chemical characterization as a fundamental preliminary step to supporting biological safety assessments by identifying potential risks.

In this paper the importance and application of an optimized chemical characterization are discussed, highlighting the possibility to save time and money by reducing the amount of *in vivo* tests needed. Finally, Eurofins Medical Device Testing's approach is also presented, providing case studies as examples.

Introduction

According to the new European Medical Devices Regulation (MDR) 745/2017 [1], a medical device is defined as *"any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) […]. A medical device does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means."*

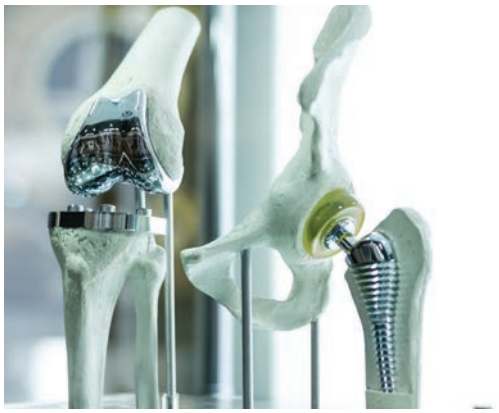
Medical devices must satisfy safety and performance requirements, and despite all their beneficial effects, there are always associated risks that require evaluation. For example, medical devices can be composed of one or more materials that have different physical and chemical properties. Even if these materials may not pose a risk for non-medical purposes (e.g., food-grade materials), their inclusion in medical devices that come in contact with the human body justifies the need for further safety evaluation. Moreover, the manufacturing and post-production processes may also introduce additional risks, as can sterilization and packaging.

When manufacturers perform a risk analysis of a medical device, in line with ISO 14971:2007 [2], its chemical characteristics are crucial factors to take into account. Here stands the importance of performing a well-suited chemical characterization, which can also set the basis for a thoughtful biological evaluation.

Biological safety evaluation

To protect humans from potential risks arising from the use of a medical device, it is cruicial to assess its biological, local and systemic effects. Moreover, for a complete biological safety evaluation, both the nature and duration of body contact must be considered. For these reasons, manufacturers refer to the ISO 10993 series, which describe the suggested approach to the biological evaluation, the endpoints that should be

considered, and the tests that could be performed. In particular, these biocompatibility tests are *in vitro* and/or *in vivo* methods used to determine the potentially harmful effects of a medical device that has direct or indirect contact with the human body.



Up to now, the most used approach has been the "check-box approach," which consists of consulting the table reported in Annex A of ISO 10993-1:2009 [3] and performing all the tests required, according to the categorization of the medical device under evaluation. Another common approach (i.e. the "one-size-fits-all") consists of indiscriminately performing the same test panel for every device.

Neither approach is suitable as they do not consider aspects of the medical device that may impact its safety (e.g. presence of different colorants, indirect contact with users, etc.). Their main limitations are that they do not allow a full understanding of the device, and could lead to unnecessary testing.

The biological evaluation of a medical device shall follow a more targeted strategy: each biological effect listed in the table should be evaluated on its own. In fact, not all tests included in the matrix may be relevant for the medical device under evaluation, as also underscored in the new FDA guidance on the use of ISO 10993-1:2009 [4]. Thus, the matrix is only a framework for the selection of endpoints for consideration and not a checklist of required biocompatibility tests.

In light of these considerations, ISO 10993-1 has been deeply revised, giving more emphasis to a crucial aspect of the biological evaluation: chemical characterization, prior to biological testing. In practice, this new emphasis translates into the addition of a new column "Physical and/or chemical information" to the table in the updated Annex A: Endpoints to be addressed in a biological risk assessment.

Why perform a Chemical Characterization?

According to ISO 10993-18:2005 [5], chemical characterization is the process of obtaining chemical information by data gathering and complementary generation, for example, by chemical testing. More precisely, it entails the use of analytical chemistry to identify and qualify the amount of chemicals in and/or extracted from a device.

There are two categories of tests to perform a chemical characterization: direct material characterization and others that evaluate substances potentially released by devices. The first group of tests evaluates the inner chemical properties of materials. The latter assesses those substances that can leach out from a device by conducting an extractable and leachable analysis (E&L) followed by toxicological risk evaluation based on the tolerable exposure levels. This data should then be evaluated by a group of experts that examine each compound, using existing literature and tools established in ISO 10993-17:2002 [6].

There are several circumstances in which chemical characterization is beneficial. Here are some examples:

Integral part of a biological safety evaluation. It supports the biological evaluation, since it provides an understanding of the intrinsic properties of the medical device. In this way, it is possible to establish which endpoints require further investigation through biological testing. With this approach, unnecessary testing may be avoided, especially the long-term ones (e.g. carcinogenicity, genotoxicity, chronic toxicity), if there is a scientific rationale to support the use of previously collected information.

Equivalence. According to ISO 10993-18:2005, equivalency is established when the composition and extractable profiles of the new material are equivalent to those of a clinically established one. Chemical characterization can provide this kind of information, in which case the new material can be evaluated as equivalent to the predicate.

Change management. When manufacturers plan to modify various aspects of a medical device, the impact of the changes on a patient's safety needs to be assessed. These changes may involve manufacturing processes, materials used, sterilization and packaging. Chemical

characterization can be used to formulate a risk assessment and to conduct a comparison study to weigh the need of further studies.

Compliance. Last but not least, regulatory reviewers and notified bodies request chemical characterization during the review process. This information provides a basis to assess conformance to the relevant standard. As already underscored, manufacturers should be aware of the changes made in Annex A of the new version of ISO 10993-1 considering the physical and/or chemical information as a prerequisite to the risk assessment.

For all these reasons, it is important that manufacturers consult with an expert when approaching chemical characterization to ensure they adequately address patient safety through a scientifically sound evaluation.

Eurofins Medical Device Testing's Approach

Eurofins Medical Device Testing offers medical device manufacturers a tailored and well-designed chemical characterization, and thus provides a strategic biological testing program. This approach may even eliminate some unnecessary biocompatibility assays, reducing *in vivo* tests and the related time and costs.

The testing strategy proposed, the amount of data required, and the depth of the investigation vary with the intended use of the medical device and are dependent upon the nature and duration of patient contact.

The aim is to leverage the materials' known properties to evaluate the related toxicological risk and assess the safety of the device on the basis of the predicted biological response of the extracted compounds. Following this assessment, possible safety gaps can be addressed with the proposal of specific tests.

Here is an example of a possible strategy (as shown in Figure 1), in which a multi-phase approach is proposed:

1. Study of the device, including its intended use, mechanism of action, production and sterilization processes, and, if known, the component's materials, as given by the manufacturer;

2. Literature research on the materials and the processes used in the production of the device;

3. Identification of the risk associated with each material and process used to manufacture the device, based on the previous steps;

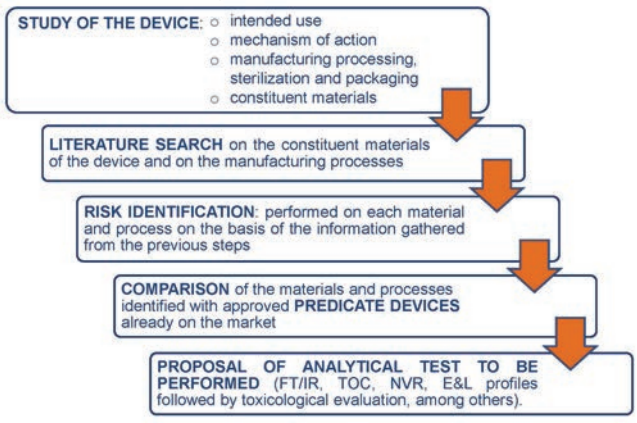
4. Comparison of the materials and processes identified for the novel device with those of any approved predicate devices already on the market;

5. Proposal of recommended analytical tests to be performed. Eurofins Medical Device Testing offers a full suite of test procedures for the chemical characterization, from Fourier Transform Infrared Spectroscopy (FT/IR), Total Organic Carbon (TOC), Non-Volatile Residue (NVR), up to E&L profiles, including toxicological evaluation. To identify extracted and leached compounds, Eurofins Medical Device Testing uses both commercial databases and an in-house proprietary database, called the Eurofins Extractables Index, which contains over 1,500 nonvolatile organic compounds that are commonly used in the production of medical devices.

It is important to underscore that this approach is not the only possible way to address the chemical characterization, since every approach is customized according to the manufacturer's needs. In fact, every scenario is unique and should be considered independently.

Overall, Eurofins Medical Device Testing provides a structured approach to perform a thoughtful chemical characterization in the context of biological safety evaluation and testing of a medical device within the risk management process.

Figure 1



Case Studies

Below are some case studies that demonstrate the benefits provided by chemical characterization:

Supplier change. When a manufacturer decides to change the raw material supplier, the manufacturer needs to evaluate the impact of the material from the new supplier in the final product. Chemical characterization is a useful tool to address this need. As an example, consider a manufacturer that changed its supplier of High Density Polyethylene (HDPE), the material constituting the mouthpiece of a device. This part of the device is the only one in contact with the human body (mucosal membrane) and for a limited time (<24 hours). According to the classification of the mouthpiece, the biological effects to be taken into account for its biological evaluation are cytotoxicity, irritation and sensitization.

In this case, chemical characterization assesses the equivalence between the "old" HDPE and the "new" one. Therefore, after extensive literature research on the safety of the material, a thoughtful characterization with FTIR and ICP screening for metals along with other chemical tests has been proposed to the manufacturer. In parallel, a cytotoxicity test on the mouthpiece coming from the new supplier has been proposed. If chemical equivalence can be demonstrated, it is reasonable to deduce that biocompatibility test results obtained on the "old" HDPE are valid for the "new" material (toxicological equivalence). As a consequence, *in vivo* tests of sensitization and irritation can be avoided, thus saving time and money.

Support to biological evaluation. It is possible to use chemical characterization data to evaluate some biological endpoints. Consider, for example, a manufacturer of metallic hip prostheses. Each one can have several components and be processed by different sub-contractors. In this case, before planning the chemical characterization, it is necessary to identify the worst case. Consider all factors involved in the manufacturing of the device, including sub-contractors, materials and processes, as well as all possible variants of these.

According to the classification of the medical device (e.g. bone-device implant with permanent contact), the endpoints to be taken into account for its biological evaluation are cytotoxicity, intracutaneous reactivity, sensitization, acute/subacute/subchronic toxicity, genotoxicity, and implantation effects. For an FDA submission, pyrogenicity, chronic toxicity and carcinogenicity should also be considered.

A chemical characterization of the medical device, including the analysis of its E&L profile, has been performed on the device representative of the worst-case scenario. As a result, data generated from the analytical test can be extended to the possible variants of the device. Then a toxicological risk assessment was performed to establish the intrinsic toxicological properties of the materials composing the device or residuals from the manufacturing process.

Thanks to this approach, enough scientific evidence has been collected and then used to evaluate the biological endpoints needed. For instance, it has been possible to justify the absence of some tests, such as subchronic toxicity, genotoxicity, chronic toxicity and carcinogenicity, since they have already been addressed by the toxicological analysis.

Conclusion

Rather than taking a check-box approach to biocompatibility testing, manufacturers should pair thoughtful toxicological risk assessment with chemical characterization data in order to evaluate a medical device and ensure patient safety. This also guarantees that a sound approach is adopted when evaluating the medical device.

Besides being a mandatory request of the regulatory bodies, a well-performed chemical characterization leads to a deep understanding of the device, thus generating ethical and economic benefits and reducing time required for the preclinical evaluation.

The more you know, the more you save!

References:

1. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices.

2. ISO14971:2007, Medical Devices- Application of risk management to medical devices.

3. ISO10993-1:2009, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.

4. U.S. Food and Drug Administration (FDA) 2016. Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process".

5. ISO10993-18:2005, Biological evaluation of medical devices - Part 18: Chemical Characterization of materials.

6. ISO10993-17:2002, Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances.