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Medical Device Biological Evaluation Reports: Relevance to the Revised ISO 10993-Part 1: 2018

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Introduction

To evaluate the safety of medical devices, a risk management approach is advocated in multiple regulatory documents, such as ISO 14791 Medical devices – "Application of risk management to medical devices" and ISO 10993 – Biological evaluation of medical devices – Part 1: "Evaluation and testing within a risk management process."[1,2] In addition, numerous global regulatory authorities also have guidance documents or directives that discuss the safety evaluation of medical devices such as the European Union (EU) Medical Device Directive 93/42/EEC, EU Medical Device Regulation 2017/745/EU, and the 2016 U.S. Food and Drug Administration (FDA) General Guidance.[3,4]

The risk management process for medical devices is outlined in Figure B.1 of ISO 14791:2012 and includes the following steps: 1) Risk Analysis; 2) Risk Evaluation; 3) Overall Risk Evaluation; and 4) Consideration of Production and Post-Production Information. This process spans the design, testing and product lifecycle of a medical device, and involves evaluating potential patient risk of both initial marketed devices and subsequent changes to materials of construction, suppliers, manufacturing or processing.

To document any potential patient risks, and to estimate and assess those risks, a biological evaluation or toxicological risk assessment is recommended by ISO 14791:2012 and ISO 10993-Part 1:2018 Standards. The basis of the biological evaluation report is the review and consideration of:

- Physical and chemical characteristics of the device materials of construction;
- Any existing toxicology or other biocompatibility data on the device components or materials of construction;
- Biocompatibility or chemical characterization testing on the device or components;
- The clinical history of use, or human exposure data from the device, components or materials of construction; and
- Intended clinical use of the device and patient exposure.

This White Paper focuses on the 2018 revision of the ISO 10993-Part 1 Standard and how it emphasizes the importance of material characterization information in biological evaluation reports.

Review of 2018 Changes to ISO 10993 Biological Evaluation of Medical Devices—Part 1: Evaluation and testing within a risk management process

To conduct a thorough evaluation, the technically competent risk assessor is required to review detailed information on all indirect and direct patient-contacting materials.

Significant changes were made in Annex A of the updated ISO 10993-Part 1 Standard (shown in **Table 1**). It should be noted that new columns have been added as endpoints for biological evaluation including:

- Physical and/or chemical information
- Material-mediated pyrogenicity
- Subacute systemic toxicity
- Chronic toxicity
- Carcinogenicity

Since potential patient safety concerns are dependent on the intended clinical use and duration of patient contact, the evaluation of these endpoints is not necessarily required for every device, with the exception of the "Physical and/or chemical information." In this case, the updated ISO 10993-Part 1 Standard mandates that information be provided on device physical properties, materials of construction, manufacturing and finishing processes that are relevant to the biological safety of the patient. A more detailed discussion of this requirement is presented later in this White Paper.

Many changes in **Table 1** involve adding the same endpoints for consideration as listed in Attachment A of the 2016 U.S. FDA General Guidance. These additions include the evaluation of "Material-Mediated Pyrogenicity;" "Acute, Subacute or Chronic Systemic Toxicity;" "Implantation;" and "Carcinogenicity" endpoints for certain devices. An endpoint can be "evaluated" using existing data (e.g., data from a device made of the same materials with clinical use), biocompatibility testing on the specific final, finished device or a rationale for why an endpoint does not require a data set (e.g., material-mediated pyrogenicity testing for a device made of a well-characterized material and with a short intended clinical use).

In the updated ISO 10993-Part 1 Standard, Annex B was replaced with the information previously contained in ISO Technical Report 14599 "Biological evaluation of medical devices—Guidance on the conduct of biological evaluation within a risk management process," which was first issued in 2016. Annex B now provides guidance on risk identification, an analysis of available scientific information (e.g.,

materials of construction, physical properties, etc.) and the development of a biological evaluation testing plan that is relevant to the data gaps, as well as the particular medical device and its intended clinical use. (Note: Annex B is considered "informative" and does not include additional requirements or change the description of those in the ISO 10993-Part 1:2018 Standard.)

Additional changes in the updated ISO 10993-Part 1 Standard include more information on the evaluation of nanoparticles and absorbable materials, information on the evaluation of "non-contacting" or "transitory-contacting" medical devices and new definitions for terms used in the ISO 10993 series. Also, the revised standard adds a cross-reference to the ISO 18562 series relative to the biocompatibility evaluation of gas pathway devices (i.e., respiratory).

Addressing the Physical-Chemical Information Consideration

According to Clause 4 of both the previous and the updated versions of ISO 10993-Part 1, an evaluation of the materials of construction, the medical device's configuration (e.g., geometry, size, surface) and any existing biocompatibility or clinical data is the fundamental start of a risk management process. In addition to Clause 1 of the revised ISO 10993-Part 1 Guidance, the risks of changes to the device over time, or after breakage, should be considered and evaluated if necessary.

To conduct a thorough evaluation, the technically competent risk assessor is required to review detailed information on all indirect and direct patient-contacting materials. To address the risk from device failure/breakage, a review of non-patient contacting materials should be conducted to determine if there are potential concerns from new or novel materials contained inside the device.

Materials information for review should include:

- The grades and specifications of the materials
- Any available supplier/manufacturer testing (i.e., biological or chemical)
- Safety Data Sheets (SDS)
- Certifications such as United States Pharmacopeia (USP), European Pharmacopoeia (Ph. Eur.) or American National Standards Institute (ANSI)
- Registration Evaluation Authorization and Restriction of Chemicals (REACH) compliance
- Restriction of Hazardous Substances Directive (RoHS) compliance
- Device Master File (MAF) numbers maintained by Notified Bodies or the U.S. FDA and the type and duration of patient contact to individual materials

Colorants are frequently incorporated or used in medical device materials, but still require a risk evaluation especially for submissions made to the U.S. FDA.[4,5] Therefore, the following colorant information should also be provided to the risk assessor when possible:

- Supplier
- SDS
- Formulation or ingredients
- Chemical Abstracts Service (CAS) or registry numbers

- Master File numbers
- Supplier testing
- The amount of colorant used in the materials (i.e., percent composition)

It is recognized that some information on colorants and materials may be considered to be proprietary by the suppliers. Even when provided with approximate composition ranges, an experienced risk assessor can still review toxicological information on the colorants or other chemicals in the biological safety evaluation.

As mentioned in the previous and updated 10993-1 Standards, it is highly relevant and important to review data, if available, on any previous clinical use of both materials and colorants in approved and marketed medical devices. Sources for these data include Post-Market Surveillance reports and Clinical Expert reports kept by the device manufacturers, databases such as the Manufacturer and User Facility Device Experience (MAUDE) maintained by the U.S. FDA and open sources from suppliers, regulatory agency websites or scientific literature.[6] From a risk management perspective, materials and/or colorants that have a demonstrated history of safe clinical use pose a much lower patient concern than new materials and/or colorants. Therefore, favorable and directly relevant clinical information can reduce or even eliminate the biocompatibility or chemical testing required to address patient safety concerns for the medical devices under consideration.

For the risk evaluation, the amount of information required and the depth of the investigation are dependent on the intended use of the material or colorant in the device/component and the duration of patient contact. For example, a wound dressing with prolonged contact to breached or compromised patient skin can be compared with a surgical mesh that is a permanent tissue implant. Since the wound dressing has a shorter treatment duration and is less invasive to the patient, a greater safety focus would be placed on the materials or colorants used in the permanently implanted surgical mesh.

In a second example, a previously approved and marketed device is being re-designed and the material suppliers of some components are being changed. In this case, information and data related to the material changes or the re-design are needed to evaluate whether the changes pose any patient or end-user risks. With respect to the data, a chemical equivalency of the new and old supplier materials could be considered in addition to limited biocompatibility testing (e.g., cytotoxicity and irritation testing) on the new final, finished device or components. As part of the risk management process, the recommended testing would be based on the intended use and patient contact of the device components that are being changed.

Devices must be designed and manufactured in such a way as to minimize the risks posed by substances leaching from the product and contacting the patient or the end user. Using biocompatible materials of construction is very important, but it is also necessary to evaluate any chemicals or materials that are possibly added to the device during the manufacturing, cleaning, packaging or sterilization processes. Potential sources of leachables include unreacted polymer materials, stabilizers, mold-release agents, cleaning chemical residues, degradation products or other processing additives. To evaluate potential leachables from a final, finished device, the risk assessor should review information on the manufacturing, processing, packaging and sterilization. Any chemicals or additional materials used in these processes should be evaluated as a source for potential patient risk. In addition, the updated ISO 10993-Part 1 Standard also requires that chemicals released during resorbable device use (i.e., intermediate and final degradants) be evaluated for potential patient safety concerns.

To address the new endpoint for "Physical and/or Chemical Information," a reasonable and comprehensive approach is to conduct a risk analysis of the potential sources of leachables and other possible patient concerns (e.g., device geometry, particles, degradants). As discussed in the updated ISO 10993-Part 1 Annex B, any available safety information, such as biocompatibility testing, chemical characterization or the clinical use history, should also be considered when creating an overall evaluation of the potential patient risks and what data are needed to mitigate these risks. The experienced risk assessor who is reviewing all information will also consider the intended clinical use and the type and duration of patient contact since these factors are pivotal in the determination of patient risk.

If the evaluation concludes that the existing data show acceptable risks, then no additional testing is warranted. An example of such a situation would be a shape change in two materials of a currently marketed device which have limited contact to mucosal membranes. No new materials of construction are being introduced and the manufacturing and processing are the same. Indeed, additional polymer material will be used in the components, but the materials are medical grade and have confirmed biocompatibility and a history of safe clinical use in that device. In this case, there is no significant potential for a patient to be exposed to additional or unknown leachables for greater than 24 hours, and therefore, any risk can be considered to be mitigated.

When there are data gaps and potential patient concerns, additional data through biocompatibility and/or chemical characterization testing are required to reach conclusions regarding safety. For instance, consider a new medical device intended for permanent implantation into tissue that is made of medical grade materials which have been used in other similar implantable devices and are marketed clinically. However, the new device geometry and size are different and require a manufacturing process that uses different molds, a silicone mold-release agent and additional cleaning steps. In this case, the new device could have potential patient concerns regarding the new shape/size, changes in the manufacturing process, the mold-release agent and cleaning chemicals. As a result, chemical characterization and biocompatibility testing on the final, finished device are recommended to mitigate potential patient concerns.

Devices must be designed and manufactured in such a way as to minimize the risks posed by substances leaching from the product and contacting the patient or the end user.

Nature of Body Contact		Duration	Biological Endpoints				
			Physico-chemical information	Cyto	Sens	Irritation Reactivity	Material-mediated Pyrogenicity
Surface Device	Intact Skin	A*	X	**E**	**E**	**E**	
		B	X	**E**	**E**	**E**	
		C	X	**E**	**E**	**E**	
	Mucosal Membrane	A	X	**E**	**E**	**E**	
		B	X	**E**	**E**	**E**	O
		C	X	**E**	**E**	**E**	O
	Breached or Compromised Surface	A	X	**E**	**E**	**E**	**E**
		B	X	**E**	**E**	**E**	**E**
		C	X	**E**	**E**	**E**	**E**
Externally Communicating Device	Blood Path Indirect	A	X	**E**	**E**	**E**	**E**
		B	X	**E**	**E**	**E**	**E**
		C	X	**E**	**E**	**E**	**E**
	Tissue, Bone, Dentin	A	X	**E**	**E**	**E**	**E**
		B	X	**E**	**E**	**E**	**E**
		C	X	**E**	**E**	**E**	**E**
	Circulating Blood	A	X	**E**	**E**	**E**	**E**
		B	X	**E**	**E**	**E**	**E**
		C	X	**E**	**E**	**E**	**E**
Implant Device	Tissue, Bone	A	X	**E**	**E**	**E**	**E**
		B	X	**E**	**E**	**E**	**E**
		C	X	**E**	**E**	**E**	**E**
	Blood	A	X	**E**	**E**	**E**	**E**
		B	X	**E**	**E**	**E**	**E**
		C	X	**E**	**E**	**E**	**E**

* Duration Abbreviations: A = Limited (< 24 hours); B = Prolonged (> 24 hours to 30 days); C = Long term (> 30 days);
Table Abbreviations: E = endpoints that must be evaluated or have a rationale; O = endpoints only recommended in the US FDA 2016 General Guidance on ISO 10993-Part 1; X = information is required for the risk assessment; carc = carcinogenicity; cyto = cytotoxicity; sens = sensitization; sys = systemic toxicity.
Blue shading indicates additions compared to the ISO 10993-Part 1:2009 Guideline, Annex A.
Bolded "E" marks pertain to recommendations made in both ISO 10993-Part 1:2018 and in the U.S. FDA 2016 General Guidance on ISO 10993-Part 1.

Biological Endpoints							
Acute Sys	Subacute Sys	Subchronic Sys	Chronic Sys	Implantation	Hemo-compability	Genotoxicity	Carc
E	**E**			**E**			
E	**E**	**E**	**E**	**E**		**E**	
E							
E	**E**			**E**			
E	**E**	**E**	**E**	**E**		**E**	**E**
E					**E**		
E	**E**				**E**		
E	**E**	**E**	**E**	**E**	**E**	**E**	**E**
E							
E	**E**			**E**		**E**	
E	**E**	**E**	**E**	**E**		**E**	**E**
E					**E**	**E**	
E	**E**			**E**	**E**	**E**	
E	**E**	**E**	**E**	**E**	**E**	**E**	**E**
E							
E	**E**			**E**		**E**	
E	**E**	**E**	**E**	**E**		**E**	**E**
E				**E**	**E**	**E**	
E	**E**			**E**	**E**	**E**	
E	**E**	**E**	**E**	**E**	**E**	**E**	**E**

Extractable and Leachable Testing

When thinking about extractable and leachables testing, it is important to understand what is trying to be accomplished when performing this type of testing.

- Extractables: Chemical additives and byproducts extracted from the device or material using exaggerated temperature and time conditions in organic solvents, water or buffers.
- Leachables: Chemicals that migrate spontaneously from materials under recommended conditions of use (simulated physiological conditions)—often a subset of extractables.

The main goal of conducting this testing is to determine what can become bioavailable to the patient when the device is challenged under elevated temperatures and aggressive solvents.

The first step when discussing extractable and leachable testing is to identify what type of extraction needs to be considered. There are two types of extractions that extractable and leachable will utilize:

- Exaggerated extraction
    - Exaggerated extraction should involve the highest temperature possible without degrading the device for a single time point that is most often 24 hours.
- Exhaustive extraction
    - Exhaustive extraction is also done at the highest temperature possible without degrading the device; however, it is a repetitive 72-hour extraction until 90 percent of all possible extractables are obtained.

Another way of thinking of this would be to conduct the extraction by covering the test article with the proper amount of solvent based on the ratios from ISO 10093-Part 12, conducting the extraction, decanting the solvent and then evaporating that solvent off to obtain a residue. The residue that is left behind is also known as the non-volatile residue or NVR. Once you have the weight of the NVR, the same test article is covered with fresh solvent and the extraction process is repeated. These steps are continued until the NVR is less than 10 percent of the initial residue weight.

When determining extraction type and conditions, clinical use and patient exposure should be taken into account. Once the extraction conditions and type is decided, the next step is to determine the proper extraction vehicles. Similar to how the extraction type is determined, clinical exposure and patient contact should be considered when choosing the extraction vehicles. Generally speaking, the various classes of extraction vehicles are polar, semi-polar and non-polar solvents. Depending on clinical use, it may be appropriate to alter the pH or use various percentages of alcohol to mimic polarity of a drug product or a bodily fluid like stomach acid.

Another consideration when determining extraction vehicles is solvent compatibility with the test article. The goal of extraction isn't to degrade the test article, but rather to challenge the device to extract any possible leachable that could become bioavailable to the patient. Therefore, many times it is necessary to run mock extractions up-front to ensure that solvents will not degrade the test article. After the extraction is complete, it will need to be analyzed for a number of classes of chemical compounds.

The major classes of compounds that need to be analyzed are:

- Volatile organic compounds (VOCs)
- Semi-volatile organic compounds (SVOCs)
- Non-volatile organic compounds (NVOCs)
- Inorganic extractables

There are other classes of compounds that need to be tested in certain situations, such as residual glutaraldehyde, formaldehyde and ionic compounds, but these four major compound classes are required on different analytical instruments (with the understanding that there could be some overlap between the three organic extractables detection methods.)

In general, the following methods are then used for analysis:

- Headspace Gas Chromatography Mass Spectroscopy (HS GC-MS) is a detection method used to analyze volatile organic compounds.
- Gas Chromatography Mass Spectroscopy (GC-MS) is the detection method used to analyze semi-volatile organic compounds.
- Ultra Performance Liquid Chromatography Mass Spectroscopy (UPLC-MS) is the detection method used to analyze non-volatile organic compounds.
- Inductively Coupled Plasma Mass Spectroscopy (ICP- MS) or Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) is used for the detection of inorganic extractables.

Another major part of extractable and leachable testing is determining how sensitized the instruments need to be in order to obtain the right information for the Toxicologist to use to address certain toxicological endpoints. The analytical evaluation threshold (AET) is defined as 'the threshold at or above which a chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment.' The AET is driven by a number things, including patient population, clinical use, number of devices a patient will be exposed to and toxicological endpoints being addressed using extractable/leachable testing.

If at the end of the extractable testing it is determined that there are

The main goal of conducting [extractable and leachable] testing is to determine what can become bioavailable to the patient when the device is challenged under elevated temperatures and aggressive solvents.

chemical(s) extracting from the device that are concerning, then simulated use extraction should be utilized to see if the chemical(s) extracting fall below a level of concern. If at that point it is still extracting at a high level, then a full leachable study is needed where a validated method for that specific chemical would have to be developed to address the chemical of concern. If a full leachable test is needed, NAMSA can supply more information on this process.

Conclusion

In the updated ISO 10993-Part 1 Standard, the endpoint, "Physical and/or Chemical Information," was added to the table in Annex A and the document mandates that information be provided on device physical properties, materials of construction, manufacturing and finishing processes relevant to the biological safety of the patient.

As part of the risk management process described in ISO 14971, the gold standard is that medical devices include materials that are biocompatible, and that the manufacturing and processing are not hazardous to patients. In this regard, the updated ISO 10993-Part 1 Standard formalizes the requirement of review and consideration of material and chemical characterization data in the assessment of medical device safety.

To address this new endpoint, a reasonable and comprehensive approach is to conduct a risk analysis of the potential sources of leachables and other possible patient concerns by reviewing detailed information on:

- All indirect and direct patient-contacting materials;
- Manufacturing, processing, packaging and sterilization procedures;
- Available biocompatibility and chemical characterization testing; and
- Any previous clinical use.

A technically competent risk assessor will review all of the available information to determine if there are potential patient safety concerns that have not been addressed by chemical characterization, biocompatibility testing or relevant clinical experience.

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