

How to Apply Extractables and Leachables to Medical Devices

Changes To ISO 10993

Recent changes to ISO 10993-1¹ have altered the landscape around the biological safety testing of medical devices. Gone is the box ticking of toxicity tests from the biocompatibility test matrix. In has come materials analysis, chemical risk analysis, analytical chemistry and toxicological risk analysis.

The name of the standard (which is not new), ISO 10993-1:2018 *Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process* is intended to reflect the philosophy that is reinforced within the document.

In it we are being told to assess the risks and manage them. The new edition has added the requirement for a chemical knowledge of every device. It also added the driver to use this knowledge to understand the potential toxicity of the device. The potential toxicity then becomes, in its turn, the driver for risk assessment which may finally lead to a testing requirement.

The principal is to list all your known materials along with any known toxicity information. You can then use this information to make a risk assessment considering these materials, always include any likely contaminants and the device function. If your product is non-invasive with short term contact and made from medically or food approved materials you might conclude that no further work is required. As the potential harm to the patient grows (through increased invasiveness and/or more prolonged contact) the need to chemically characterise the final product increases. This is where ISO 10993 part 18 and extractables and leachables start to become relevant. Traditional in-vivo studies for toxicity end points need only be applied if other sources of information are not available.

Biocompatibility Matrix

The ISO 10993-1 biocompatibility matrix now provides a guide to the selection of information requirements. Chemical analysis has now been added to every category. This does not always mean that testing is required, but knowledge of potential toxicity is obligatory.

When applying the philosophy of the biocompatibility matrix it is clear that the rigorousness of chemical analysis and any associated toxicological risk analysis can be adapted to the application of the device.

Hence unbroken skin contact would require less intensive extraction and investigation of available chemical migrants. Whilst a long term implant would need exhaustive extraction and analysis with a thorough risk analysis of all materials identified.

Material Characterisation³ - Extractables and Leachables⁴

Material characterisation as described in ISO 10993-18² includes consideration of the chemical materials present and also morphology and the nature of the surfaces. The surface investigation may be concerned with surface features that encourage ingrowth or bacterial colonisation. Also, there might be concerns with particular surface chemistry or catalytic properties of the surface. Methods of investigation could include electron microscopy, elemental analysis, infra-red spectroscopy or other techniques.

Body Contact		Contact Duration Days	Testing Required														
			Chemical Characterisation	Cytotoxicity	Sensitisation	Irritation	Pyrogenicity	Acute Toxicity	Subacute Toxicity	Sub Chronic Toxicity	Genotoxicity	Implantation	Haemocompatibility	Chronic Toxicity	Carcinogenicity		
Surface Devices	Skin	<=1	x	x	x	x											
		1-30	x	x	x	x											
		>30	x	x	x	x											
	Mucosal Membrane	<=1	x	x	x	x											
		1-30	x	x	x	x			x	x			x				
		>30	x	x	x	x			x	x	x	x	x		x		
	Breached or compromised surfaces	<=1	x	x	x	x	x	x	x								
		1-30	x	x	x	x	x	x	x	x			x				
		>30	x	x	x	x	x	x	x	x	x	x	x		x	x	
Externally Communicating Devices	Blood path indirect	<=1	x	x	x	x	x	x						x			
		1-30	x	x	x	x	x	x	x					x			
		>30	x	x	x	x	x	x	x	x	x	x	x		x	x	
	Tissue, Bone, Dentin	<=1	x	x	x	x	x	x	x								
		1-30	x	x	x	x	x	x	x	x			x				
		>30	x	x	x	x	x	x	x	x	x	x	x		x	x	
	Circulation blood	<=1	x	x	x	x	x	x	x						x		
		1-30	x	x	x	x	x	x	x	x			x		x		
		>30	x	x	x	x	x	x	x	x	x	x	x		x	x	x
Implant Devices	Tissue, Bone	<=1	x	x	x	x	x	x									
		1-30	x	x	x	x	x	x	x			x		x			
		>30	x	x	x	x	x	x	x	x	x	x		x		x	
	Blood	<=1	x	x	x	x	x	x	x						x		
		1-30	x	x	x	x	x	x	x	x			x		x		
		>30	x	x	x	x	x	x	x	x	x	x	x		x	x	x

The primary study will always be an investigation of materials released from the medical device in use. This is also the idea that was used in the traditional testing, using extracts from device in *in-vivo* testing. In chemical analysis this is often described as an extractables and leachables study. The requirement for the assessment of migrating materials from a pharmaceutical container is fairly clearly defined, for medical devices we return to the standards and the risk analyses.

The leachables are described in ISO 10993-17⁵ as ‘released constituents that potentially contact the individual during clinical use’. The extractables include additional entities that can be forced out of the materials of construction, in the ISO 10993-17 definition ‘constituents that can be extracted in the laboratory’. The reason for identifying and quantifying the extractables, in pharmaceutical container studies, is that there is a risk of them transferring into the formulation at some point during its storage. Similarly the reason for examining extractables in medical devices is that they might become leachable at some point during the device’s lifetime.

When designing a study it should be borne in mind that there may be multiple chemicals in the production process (mould

release, processing and machinery oils, solvents, UV or other adhesives). Also, many of the specified materials (particularly plastics and adhesives) may contain undeclared additives including: activators/ accelerators, catalysts, colours or enhancers, lubricants, scratch protection, side reaction products, residual monomers, UV or other stabilisers... the list is long.

The leachables concept transfers quite well to medical devices. The adhesive on ECG electrodes has only dry skin contact. The ‘in use leachables’ are only those materials that could transfer to the skin over the period of a few days. If the electrode is replaced after three days, the patient is subjected to a new dose of leachables. The idea of forcing extractables from the electrode is not very useful here. However for a long term cerebral implant there is a possibility of chemicals which are more difficult to extract migrating into the patient. Here the concept of ‘simulated use’ leachables is introduced. Clearly it is not possible to wait for many years for the extractable to migrate into solution for analysis.

ISO 10993-12⁶ gives us the extraction conditions (area to volume ratio, time and temperature, solvent polarity), but may not go far enough for more invasive devices.

Therefore forced extraction is used, the strength of which (whilst being based in ISO 10993-12) can be adjusted according to the environment and duration of use. Hence, 'simulated use extract'. As we go up the invasiveness scale we increase the strength of the solvents and consider increasing the extraction times and temperatures. Consider because we are only interested in materials that will be present in use not degradation products produced in the extraction process.

Selection of Extractable and Leachable Analysis According to Patient Contact

Following the above review it is logical to allocate different levels of analysis to meet the needs of the biocompatibility matrix. (A brief description of the analytical methods is given at the end of this document).

Level 1 - Medical Device Transient Contact

- Is suitable for surface contacting devices with transient or short term use.
- Initial gathering of chemical data
- Two extraction polarities, 37° C for 72 hours.
- Analysed according to standard protocols
- Analyses GFAAF, GC-MS, HPLC-MS
- Phthalate reference standard only
- Toxicological risk analysis only if unexpected materials of concern found.

Level 2 - Medical Device Prolonged or Invasive Contact

- Is suitable for medium risk devices.
- Initial gathering of chemical data
- Material review
- Two extraction polarities, 50° C for 72 hours.
- Analysed according to standard protocols with method verification
- Phthalate reference standard, plus any substances referenced in material review
- ICP-MS, GC-MS, GC/HS-MS, HPLC-MS
- Toxicological Risk Analysis

Level 3 - Medical Device Permanent Contact

- Implant and repeat use devices.
- Comprehensive gathering of chemical data MET
- Material review and risk analysis
- Specific study design and protocol using validated methods
- Method development if required.
- Include comparative standards for materials of concern
- Three extraction polarities, 50° C for 72 hours plus exhaustive or special extraction, sample concentration.
- Reference standards as specified in material review
- May include degradation studies (ISO 10093-13)
- ICP-MS/AAF, GC/HS-MS, GC-MS, LC-MS, LC-TOF.
- Toxicological Risk Analysis

Table 1 – Standard surface areas and extract liquid volumes

Thickness mm	Extraction Ratio (surface area or mass/volume) ±10%	Examples of Forms of Materials
<0,5	6 cm ² /ml	Film, sheet, tubing wall
0,5 to 1,5	3 cm ² /ml	Tubing wall, slab, small moulded items
>1,0	3 cm ² /ml	Larger moulded items
>1,0	1,25 cm ² /ml	Elastometric closures
Irregularly shaped solid devices	0,2 g/ml	Powder, pellets, foam, non-absorbent moulded items
Irregularly shaped porous devices (low-density materials)	0,1 g/ml	Membrane textiles

Note: While there are no standardised methods available at present for testing absorbents and hydrocolloids, a suggested protocol is as follows:

- determine the volume of extraction vehicle that each 1,0 g or 1,0 cm² of material absorbs
- then, in performing the material extraction, add this additional volume to each 1,0 g or 1,0 cm² in an extraction mixture

Table 2 – Standard Extraction Conditions (ISO 10993-12)

Temperature	Extraction Time
(37 ± 1) °C	72 ± 2 hours
(50 ± 2) °C	72 ± 2 hours
(70 ± 2) °C	24 ± 2 hours
(121 ± 2) °C	1 ± 0.1 hours

Toxicological Risk Analysis

The analytical chemistry produces information on which materials are present and in what quantities. To be useful this information must be interpreted in terms of the toxicity end points given in the biocompatibility matrix. If no materials of concern are found or the patient contact is transient then this can be quite simple assessment. As more materials are identified and the patient contact becomes more intense the requirement for a Toxicological Risk Analysis increases. This analysis is the domain of a Registered Toxicologist. Who takes each material found and calculates the patient dose per 24 hours and over the product lifetime. A variety of information sources are then used to quantify the potential toxicity of the materials individually and combined.

Conclusion

A knowledge of any chemicals released, in use, by a device is now required by ISO 10993. This is now listed in the testing matrix for every category of device. Materials characterisation is not the only route to obtaining this information, but it is the most likely method to find unexpected materials. The vigour of application of chemical analysis should be tailored to the body contact and risk analysis for the device. Often the chemical information can address most of the toxicity end points without any need for animal testing, through a Toxicological Risk Analysis.

References

- 1. ISO 10993-1:2018**
Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
- 2. ISO 10993-18:2005**
Biological evaluation of medical devices – Part 18: Chemical characterization of materials
- 3. <https://www.met.uk.com/medical-device-testing-services/biocompatibility/chemical-characterisation>**
- 4. <https://www.met.uk.com/4dii-testing-and-analysis-of-extractables-and-leachables>**
- 5. ISO 10993-17:2002**
Biological evaluation of medical devices – Part 17: Establishment of allowable limits for leachable substances
- 6. ISO 10993-12:2012**
Biological evaluation of medical devices – Part 12: Sample preparation and reference materials
- 7. ISO 21726:2019**
Biological evaluation of medical devices – Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents



Mark Turner is Managing Director of Medical Engineering Technologies, which provides a wide range of services to engineers and project managers in the medical device industry. Turner founded MET in 1997 after 12 years of project management and device design with Smiths Medical. He has also worked as a perfusionist in the cardiac unit of Kings College Hospital (London, UK) providing experience of the application of medical devices first hand. He received a BSc in Chemistry (with Biochemistry) from the University of Wales in 1983 and has also studied astronomy, business administration, cosmology and opto-electronics.

Mark Turner
Managing Director MET

A Brief Description of Analytical Methods

LC-MS

Liquid chromatography – mass spectroscopy is used to analyse materials that are liquid at normal temperatures. Solvents are used to extract these materials from a device or container. The solvent containing the migrated materials is then injected into a tube containing a separation media which divides up the chemicals (this works just like blotting paper and ink). The materials are then presented to the mass spectrometer individually for analysis by mass. The spectrometer has similar technology an old fashioned TV with a cathode ray tube. The molecules are broken down by the electrons in the tube and accelerated towards a target. The time taken to arrive is related to the mass of the molecule and can be used to identify the chemical.

MET also has a variant of this machine called an LC-TOF. This Time of Flight instrument is extremely precise and helps in identifying unexpected materials by revealing their exact masses.

GC-MS

Gas chromatography – mass spectroscopy. This technology follows the same pattern as the LC. It analyses materials that are gaseous or volatile at normal temperatures.

GC-MS/HS

This instrument is a GC-MS complimented by a heating system at the entry point to the chromatography tube. This allows it to analyse materials with greater volatility (lower boiling point) than those normally found in gas chromatography and liquid chromatography systems. It is called a Headspace GC-MS.

GFAAF

Graphite Furnace Atomic Absorption. This instrument is loads of fun. It works in the same way as dropping salt onto your gas cooker's flame. The flame will be turned from blue to orange. The orange colour is unique (actually its wavelength is) to the sodium in the salt. Every metal has its own range of colours and can be identified and quantified by this method. This is actually how we know the composition of stars, planetary atmospheres and interstellar gases. Movement of stars away from us stretches the wavelength of the light to be more red than we normally expect for the 'metals' present. This 'red shift' tells us the speed of the stars movement.

ICP-MS

This analysis is similar to the atomic absorption. The equipment is less sensitive but works better for analysing multiple metals.