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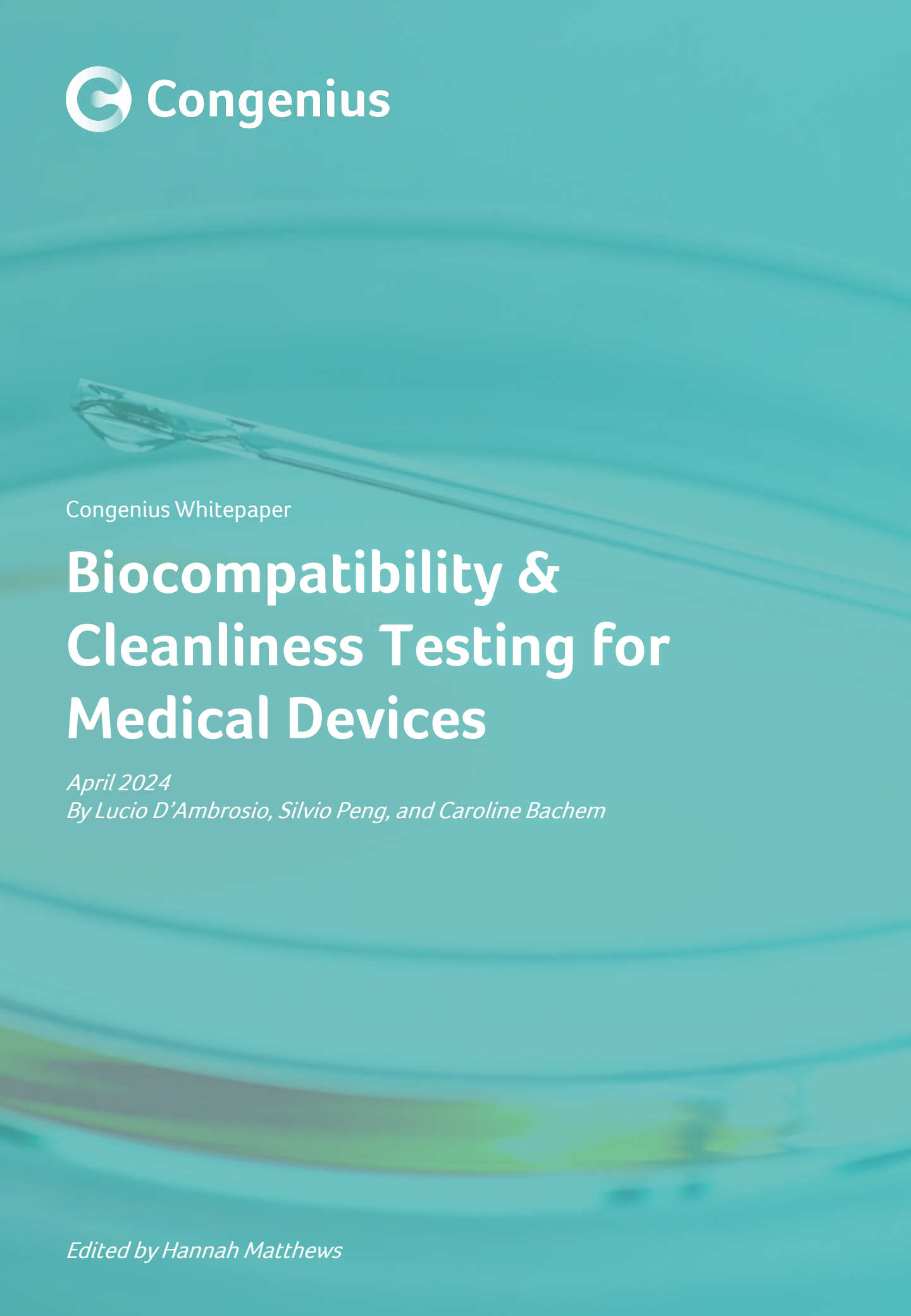

Congenius Whitepaper

Biocompatibility & Cleanliness Testing for Medical Devices

April 2024

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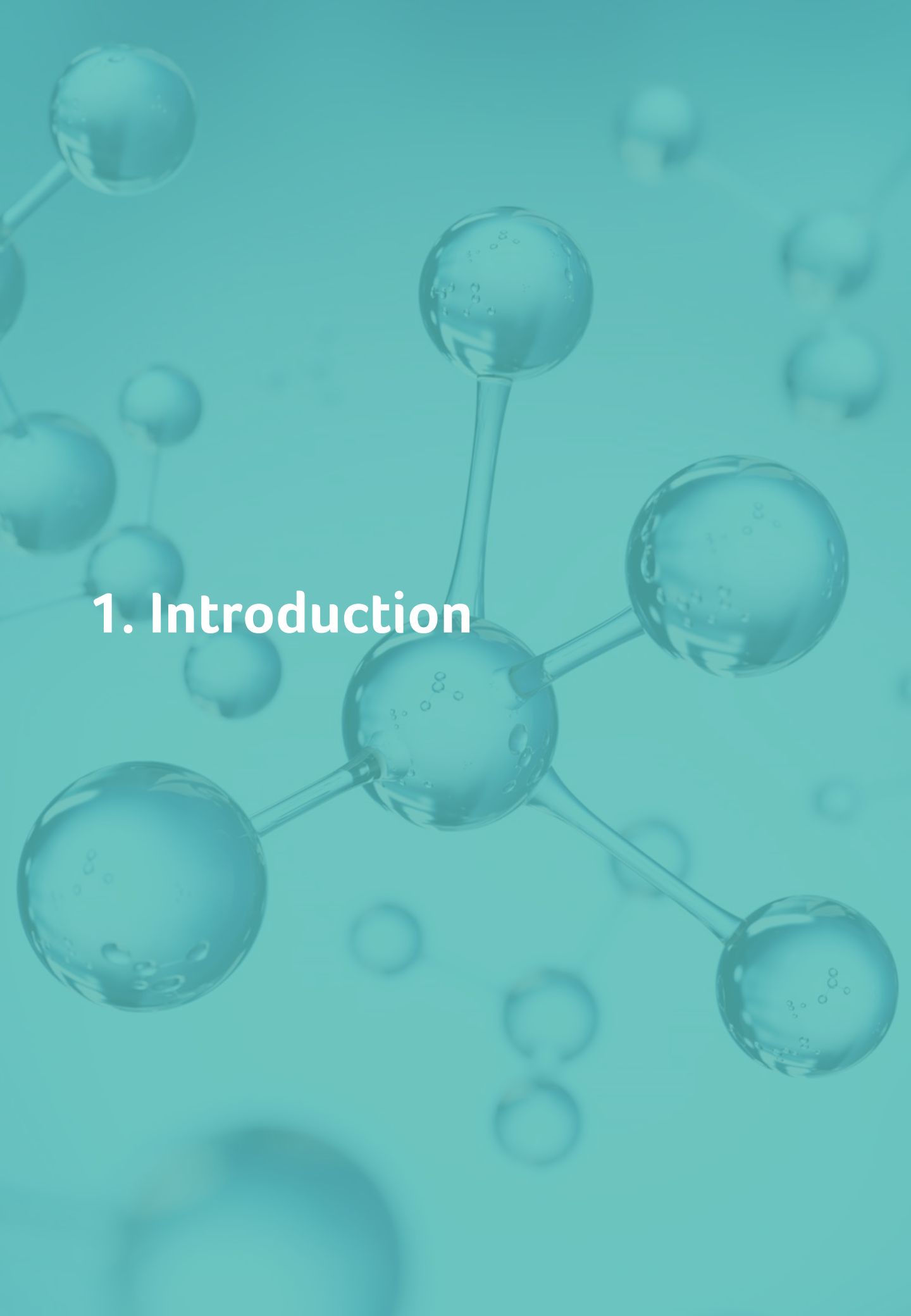


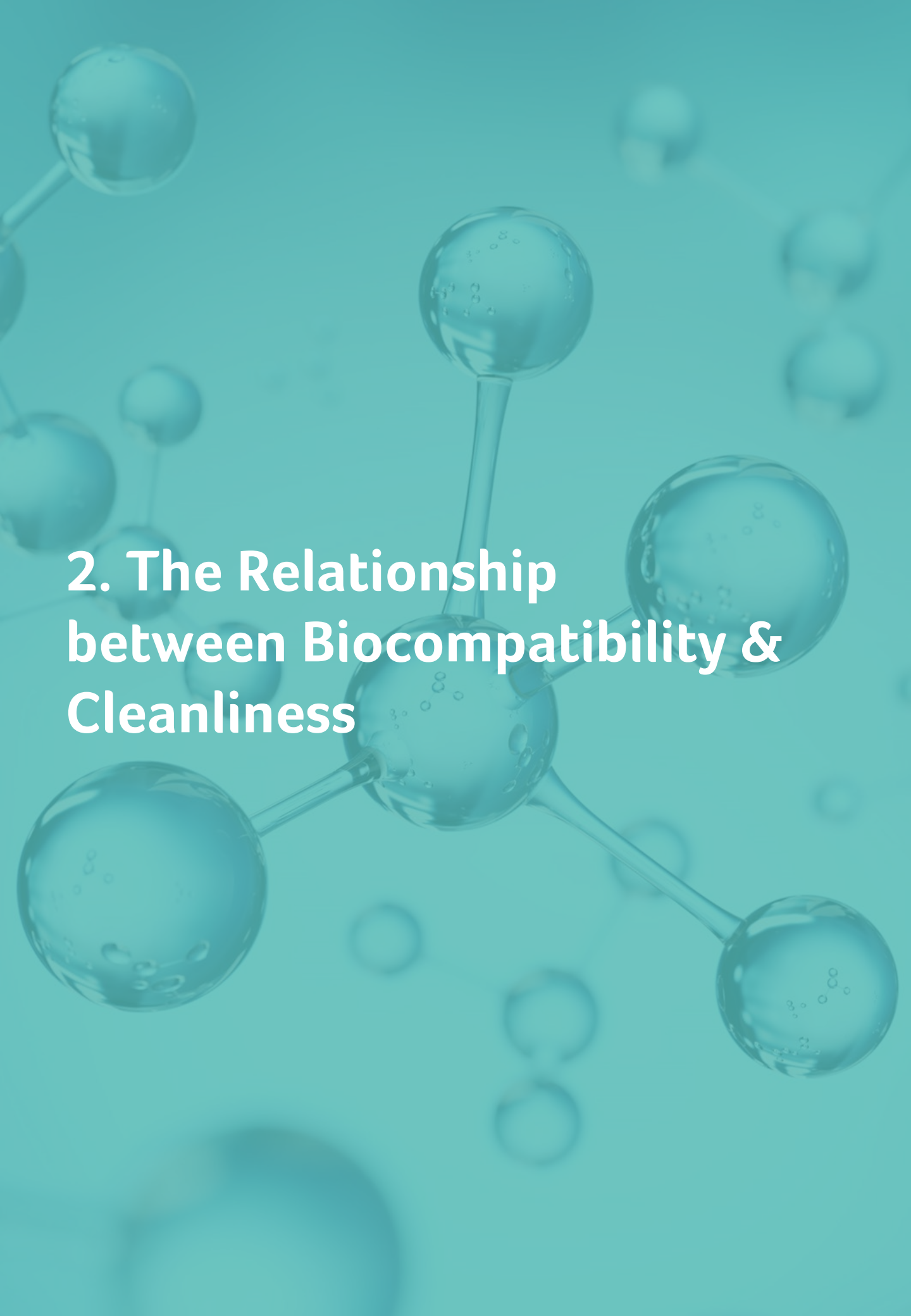
1. Introduction

Introduction

In the realm of medical technology and innovation, the development and production of safe and effective medical devices is of paramount importance. Ensuring the well-being of patients and users requires a comprehensive understanding of various factors that contribute to the performance and safety of these devices. Two critical aspects that are often discussed in this context are **biocompatibility** and **cleanliness**.

Whilst these terms might seem similar, they **represent distinct concepts** that play unique roles in the assessment and regulation of medical devices. Medical device developers and manufacturers must prioritise both biocompatibility and cleanliness to uphold the highest standards of patient care and safety. However, with a plethora of testing philosophies, test methods, and no globally defined limit values, combining biocompatibility and cleanliness testing can prove difficult. Furthermore, it is often the case that manufacturers and suppliers have a different understanding regarding the requirements for cleanliness levels.

This whitepaper elucidates the relationship between biocompatibility and cleanliness, highlights the key differences between the concepts, and sheds light on their significance in the field of medical devices.



2. The Relationship between Biocompatibility & Cleanliness

The Relationship between Biocompatibility & Cleanliness

Biocompatibility refers to the ability of a medical device to perform with an appropriate host response, i.e., interact with living tissues, cells, and biological systems, without causing adverse reactions.

The goal of ensuring biocompatibility is to prevent any potential harm that might arise from the interaction between the device and the human body. This is particularly important given the diverse range of medical devices (from simple bandages to complex implantable devices), that come into direct contact with patients. According to the ISO 10993 series, biological evaluations to determine a medical device's compatibility with the biological environment must be performed taking into consideration the nature and duration of patient contact.

Cleanliness refers to the acceptable levels of contaminants, residues, and particles present that could compromise the safety and efficacy of a medical device.

Maintaining cleanliness is crucial to prevent adverse reactions and other complications that might arise due to the presence of foreign substances on the device's surface or within its components, since contaminants, residues, and particles might impact the biocompatibility of the devices. In addition, a clean device is a prerequisite for effective sterilization.

Key aspects of ensuring cleanliness include:

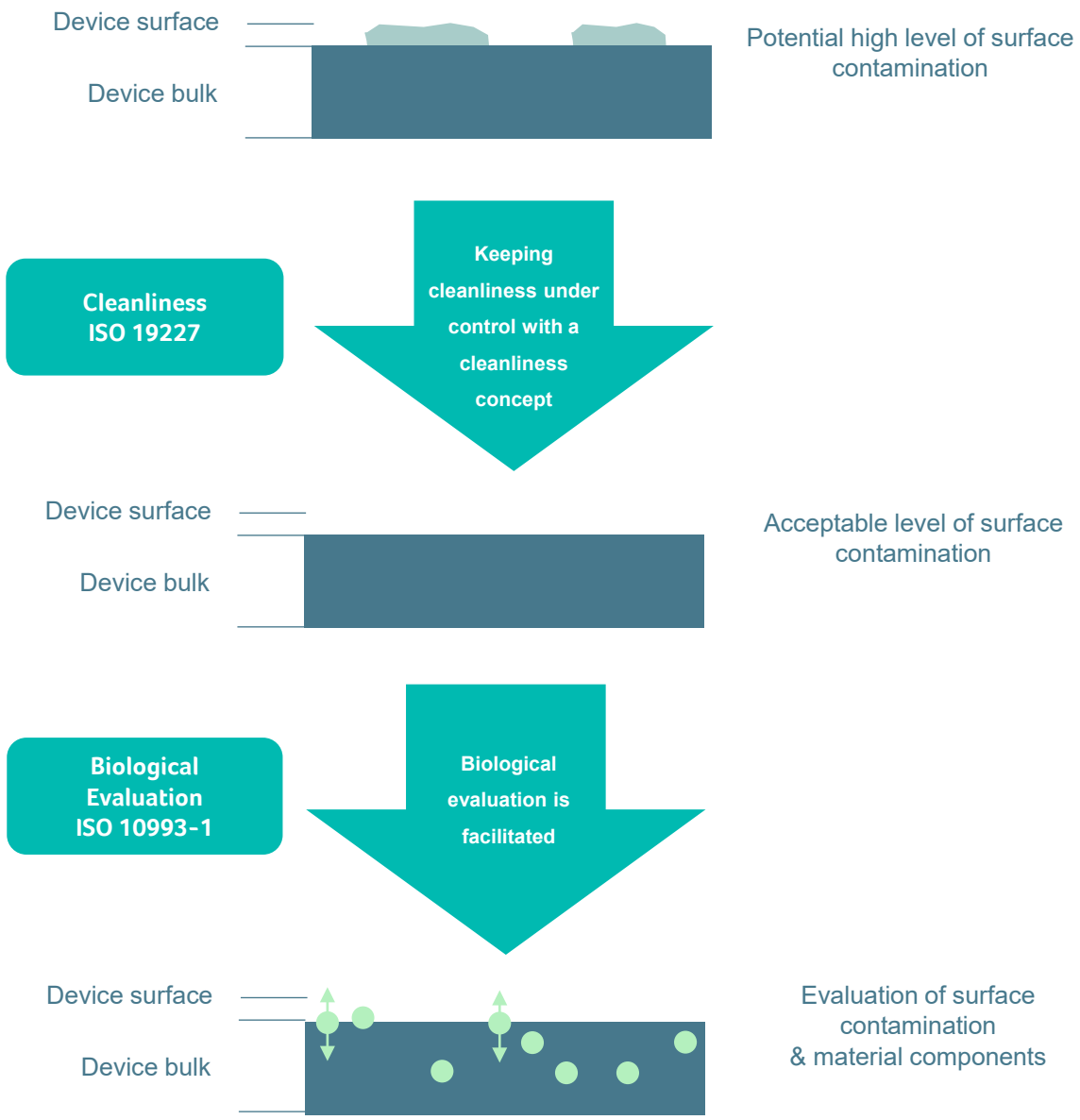
Cleaning validations: These validate the effectiveness of cleaning processes, ensuring that residues and contaminants are consistently removed to achieve acceptable levels.

Cleanliness monitoring: After the validation, a monitoring interval must be defined to ensure the continuous cleanliness level for the monitored parameters. Setting alert levels below the effective acceptance criteria might allow for recognising potential trends in contamination before exceeding them.

Biocompatibility and cleanliness are distinct yet interrelated aspects of ensuring the safety and performance of medical devices. Biocompatibility focuses on assessing the device's compatibility with biological systems as part of the biological evaluation (verification at product level), while cleanliness ensures the acceptable levels of contaminants that could compromise the manufacturing quality (validation and monitoring at process level). Both are critical components of comprehensive quality assurance processes that safeguard patients and users from potential harm.

The Relationship between Biocompatibility & Cleanliness

By reducing surface contamination through a specific cleanliness concept adapted for the product portfolio, biological evaluation is facilitated:



The Relationship between Biocompatibility & Cleanliness

The huge diversity in medical devices makes the definition of a procedure with clear limit values very challenging.

Therefore, the cleanliness and biological evaluation concept must be adapted from the given standards and guidance to each product portfolio. In addition, the expectations from authorities around the world differ regarding certain details, so a well-planned concept based on a sensible risk analysis and appropriate data collection is crucial for a thorough assessment.

Based on the well-known tabular visualisation of the endpoints to evaluate in a biological evaluation (Table A.1 in ISO 10993-1), the **physical and / or chemical information** is a relevant endpoint that must be considered for all medical device categories. Depending on the nature and duration of body contact, different endpoints need to be additionally considered (note that the requirements of the FDA guidance and ISO 10993-1 do not fully overlap).

Medical device categorization by				Endpoints of biological evaluation													
Nature of body contact		Contact duration	Physical and /or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity	Acute systemic toxicity	Subacute toxicity	Subchronic toxicity	Chronic toxicity	Implantation effects	Hemocompatibility	Genotoxicity	Carcinogenicity	Reproductive / developmental toxicity	Degradation
Category	Contact	A – limited B – prolonged C – long term															
Surface medical 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		E	E			E					
		C	X	E	E	E		E	E	E	E	E		E			
	Breached or compromised surface	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E	E		
Externally communicating medical device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue / bone / dentin	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulating blood	A	X	E	E	E	E	E					E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
Implant medical device	Tissue / bone	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Blood	A	X	E	E	E	E	E				E	E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

Since the physical / chemical information is relevant for the assessment of biocompatibility, it is logical to not only consider it with the biological evaluation but also monitor it in connection with the manufacturing process. This requires a cleanliness concept adapted for the specific product portfolio.

3. Potential Contaminants & Material Components

Potential Contaminants & Material Components

Below and on the following page, we show examples of potential contaminations and interactions that should be considered.

Examples of contaminants from the manufacturing process (related to processing aids)

- Processing oils
- Cleaning agents
- Polishing media
- Passivation agents
- Blasting media
- Bacterial endotoxins
- Viable microorganisms

Examples of substances of a medical device that can be released during intended use (related to material components)

- Pigments in polymers
- Softening of polymers
- Metal ions of metal alloy
- Corrosion residues
- Decomposition substances of polymers
- Debris and particles

These contaminants might be detected by various analytical methods. Let's briefly look at the difference between leachables and extractables at this point, as it is typically difficult to distinguish between the two in analytical findings:

- **Leachables** are substances that are released from a medical device or material during its clinical use

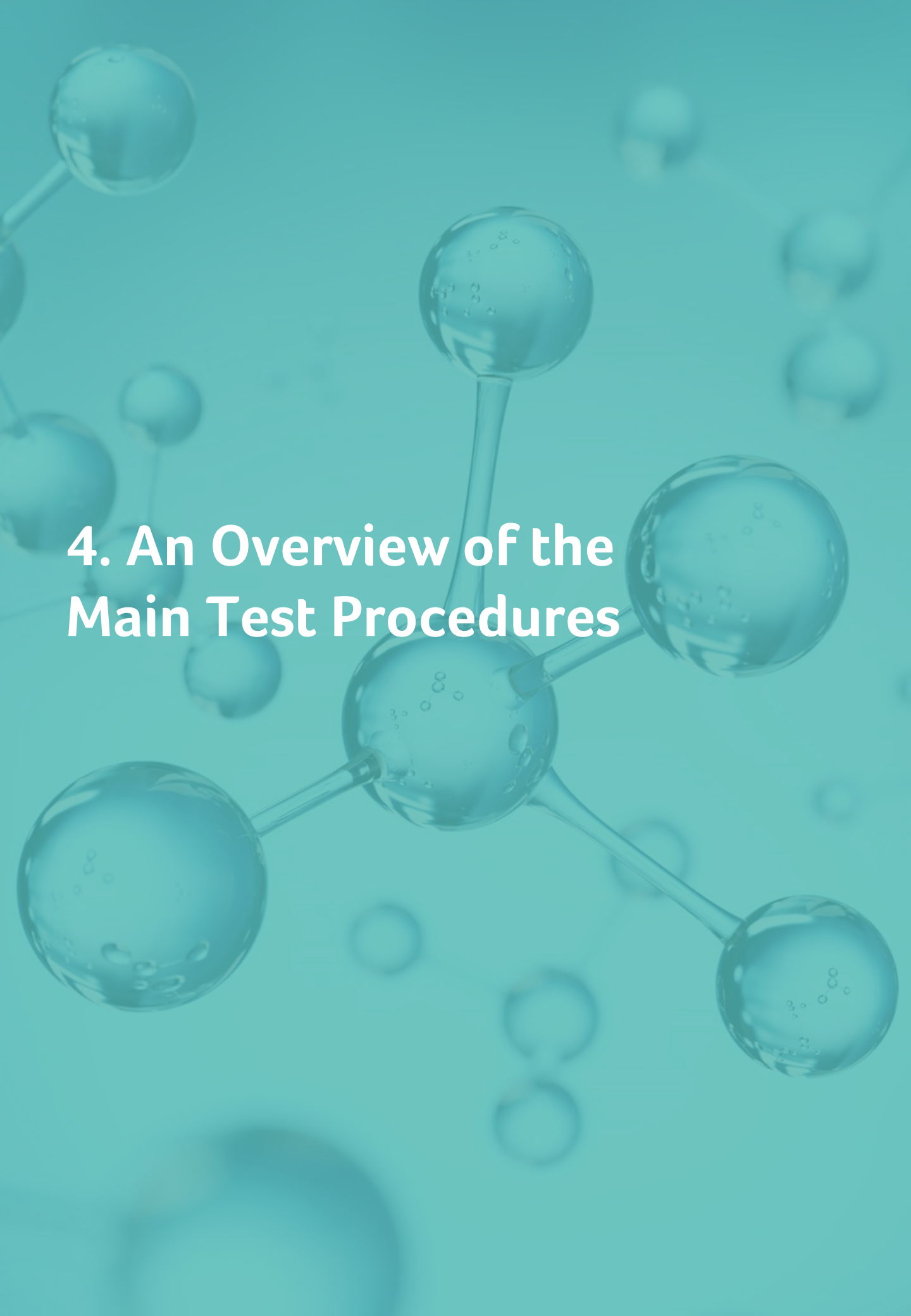
- **Extractables** are substances that are released from a medical device or material of construction when the medical device or material is extracted using laboratory extraction conditions and vehicles

Potential Contaminants & Material Components

Furthermore, the potential contaminants can be classified in chemical / physical / biological categories as follows:

Contamination Category	Description
Organic substances	Substances that contain carbon in the molecule (with a few exceptions)
Inorganic substances	Substances that do not contain carbon in the molecule (with a few exceptions)
Particles	Insoluble, solid particles, which can be organic or inorganic in origin
Microorganisms	Microorganisms such as bacteria, viruses, and fungi
Endotoxins	Endotoxins are components of the cell from Gram-negative bacteria, which can cause severe immune responses in patients

The risk of potential contaminants from the manufacturing process and release of material components during the intended use depends on the medical device materials - such as polymers, metals, ceramics, and fluid solutions. Various manufacturing operations are applied for each of the material groups and in addition, different materials can be combined in one medical device. This can make the risk analysis very complex. As such, to track potential contaminants, adequate testing methods must be applied.



4. An Overview of the Main Test Procedures

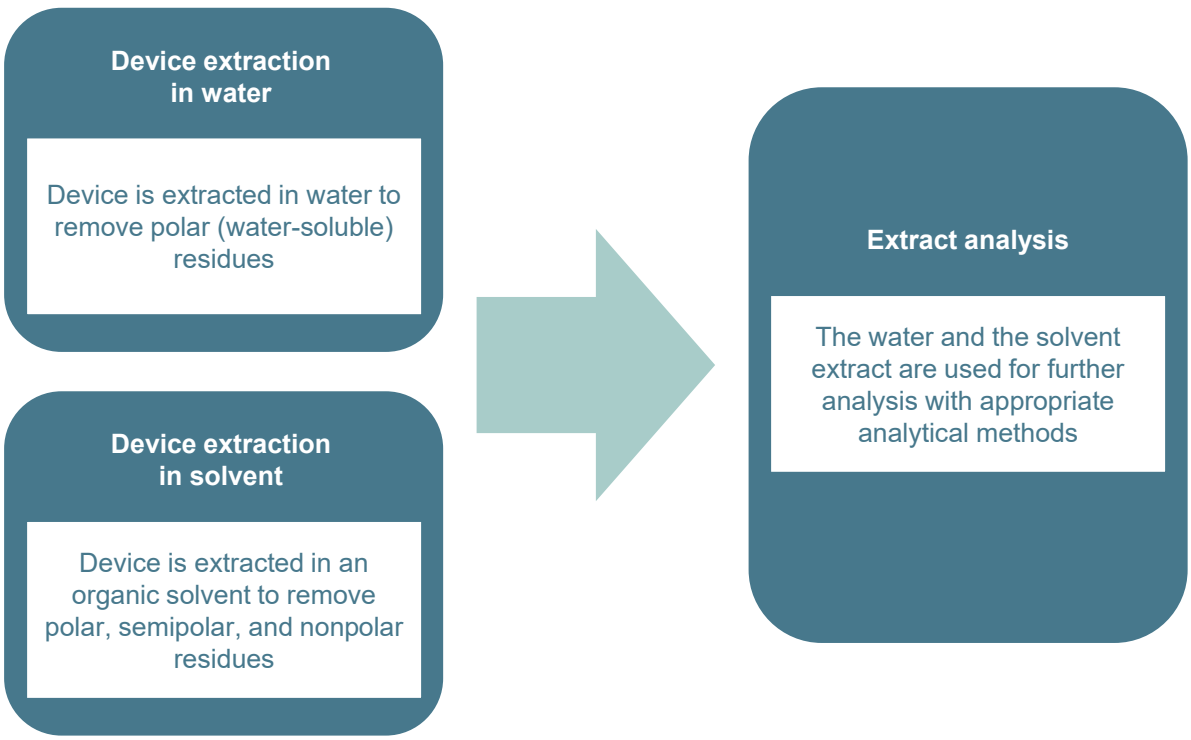
An Overview of the Main Test Procedures

Due to the diversity of potential contaminations, with correspondingly different chemical / physical properties, multiple extraction solvents and analytical techniques must be used to ensure the highest capture of substances.

As demonstrated in the figure below, the potential contaminants must be extracted from the medical device using solvents of different polarities to ensure removal of a wide spectrum of substance polarity.

The extraction should ensure that independent of geometrical features, the relevant surface of the device is in contact with the solvent. In general, polar, semi-polar, and non-polar solvents are used. In the case of polar solvents, a distinction is made between water and organic solvents, since only the aqueous extract can be used for certain analytical methods.

The extracts are then analyzed via appropriate analytical methods.



An Overview of the Main Test Procedures

In general, a distinction can be made between different types of analytical methods:

Semi-quantitative

Amount of detected substances can be estimated by comparison with surrogate substances (similar in chemical composition)

Quantitative

Amount of detected substances can be reported

Qualitative

No information about the residues amount possible. Indication of the presence of a residue by measuring, observing, or triggering a reaction or signal.

Characterizing

Information about chemical composition can be made. Depending on availability and quality of databases, identification possible.

An Overview of the Main Test Procedures

The table below illustrates a compilation of typical analysis methods used for cleanliness according to ISO 19227 or chemical characterization according to ISO 10993-18. Depending on targeted potential contaminants, additional or adapted methods (e.g., other detectors to change from semi-quantitative to quantitative) can be applied.

Method	Description	Analysis method
Visual Inspection	Via visual inspection, residues or discolorations can be observed.	**Qualitative**
TOC (Total Organic Carbon)	Measures the total amount of carbon present in organic compounds within a sample. Used to assess cleanliness and potential contamination in medical devices by detecting the sum of organic residues solved in water.	**Quantitative**
THC (Total Hydrocarbons)	Quantifies the total amount of hydrocarbons present by detecting organic hydrocarbon substances in a solvent extract of a medical device.	**Semi-quantitative**
Ionic Residues	Calculated residues from the measurement of the conductivity of a water extract.	**Semi-quantitative**
Gravimetry	Measures the mass to determine the amount of residues present extracted from a medical device.	**Quantitative**
GC-MS (Gas Chromatography-Mass Spectrometry)	Separates and analyzes compounds in a sample extract to detect and quantify semi-volatile organic compounds (SVOC) in a water or solvent extract. By using the mass spectrometry detector, it is possible to characterize the detected substances.	**Semi-quantitative** **Characterizing**
HS-GC-MS (Headspace Gas Chromatography-Mass Spectrometry)	Separates and analyzes compounds in a sample extract to detect and quantify volatile organic compounds (VOC) in a water or solvent extract respectively direct from a solid sample. By using the mass spectrometry detector, it is possible to characterize the detected substances.	**Semi-quantitative** **Characterizing**
LC-MS (Liquid Chromatography-Mass Spectrometry)	Separates and analyzes compounds in a sample extract to quantify non-volatile organic compounds (NVOC) in a water or solvent extract. By using the mass spectrometry detector, it is possible to characterize the detected substances.	**Semi-quantitative** **Characterizing**
IC (Ion Chromatography)	Separates and analyzes ions in a sample, commonly used to detect and quantify inorganic and organic ions.	**Quantitative**
ICP-MS (Inductively Coupled Plasma-Mass Spectrometry)	Detects and quantifies trace elements, metals, and heavy metals in a sample of water extract at very low concentrations.	**Quantitative**
REM-EDX (Scanning Electron Microscopy with Energy-Dispersive X-ray Spectroscopy)	Allows imaging of surface structures and elemental analysis of materials (e.g., solid residues). It gives information about mainly the composition and elemental distribution of residues.	**Characterizing**
XPS (X-ray Photoelectron Spectroscopy)	Analyzes the surface chemistry of residues by measuring the energies of emitted electrons. It is used to characterize the chemical element composition of residues (e.g., solid residues or particles). With the information, details of the chemical structure can be estimated.	**Characterizing**
FTIR (Fourier Transform Infrared Spectroscopy)	Identifies chemical compounds based on their absorption of infrared light. Used in medical device testing for material identification by comparing the infrared spectra with a reference or database.	**Characterizing**
Particle Counting	Detects and quantifies the number and size distribution of particles in a sample extract.	**Quantitative**
Cytotoxicity	Assesses if there is any effect causing cell damage or cell death. Such an effect might originate from contamination or material components.	**Qualitative**
Bioburden	Quantifies the number of viable microorganisms present on or within a medical device.	**Quantitative**
Endotoxins	Measures the presence and concentration of bacterial endotoxins.	**Quantitative**

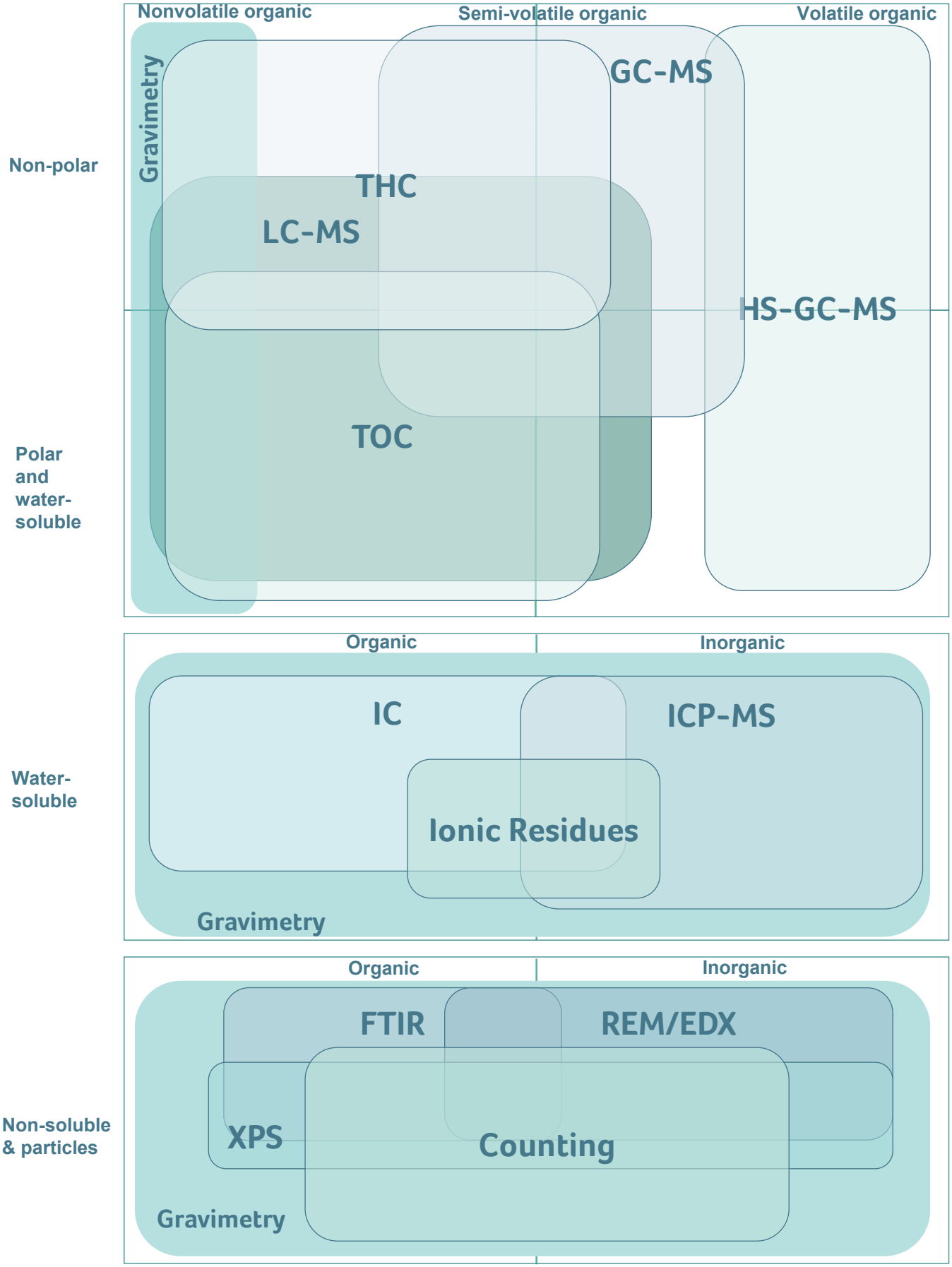
An Overview of the Main Test Procedures

The visualization on the next page attempts to qualitatively relate the commonly used wide range of analytical methods to the different potential categories of residues.

In terms of cleanliness, the focus is primarily on the extractables - that means on the substances that are released when the medical device is extracted using laboratory extraction conditions and vehicles. Whereas, for the biological evaluation, leachables might additionally be included in order to cover clinical relevance.

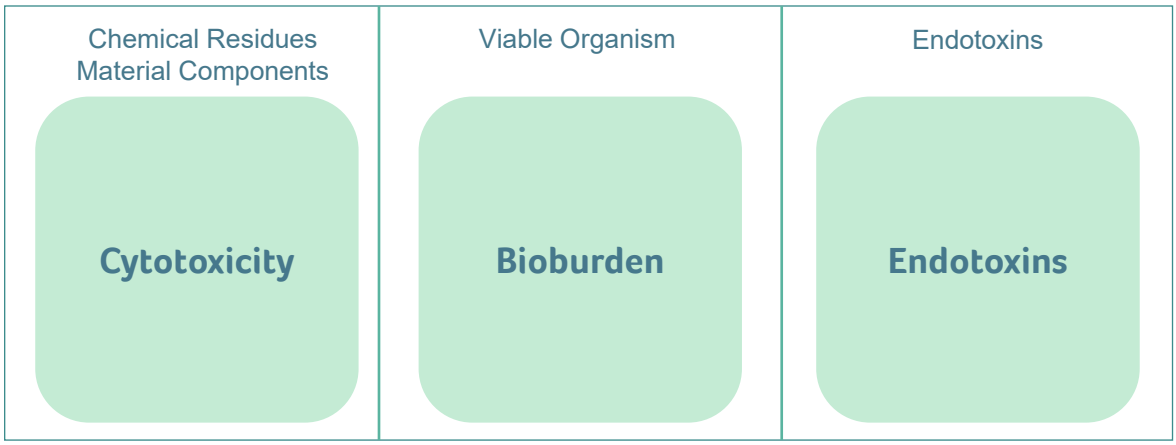
The simplified visualized schematic overview shows how important it is to perform different methods to cover potential residues. It also shows some overlap and possible gaps.

An Overview of the Main Test Procedures



An Overview of the Main Test Procedures

The following biological test methods are illustrated separately to present them in relation to each other and to separate them from the physical / chemical test methods outlined on the previous page:



Whilst we have presented a compilation of potential analysis approaches, this variety is not exhaustive. Analysis methods are continuously improved and new methods might be introduced.

It is worth noting that Cytotoxicity is a special case, as this test is used both as part of biological evaluation (ISO 10993-5) and to determine cleanliness (ISO 19227). Here, the use must be clearly differentiated for which purpose the test is performed.

The combination of methods depends heavily on the specific research question, the analyzed sample, the needed sensitivity (LOD and LOQ) and, fundamentally, technical feasibility and limitations (e.g., incompatibility of polymer with extraction solvent).

As shown in the table on page 15, a broad number of analyses is often required to ensure that no toxicologically relevant amounts of contaminants, compounds, debris, or degradation substances are released from the medical device during the intended use.

The testing strategy including potential omission of tests must be justified within a complete risk assessment. This is one of the most important steps that can be taken to reduce testing effort and save costs.

5. Aligning Manufacturers & Suppliers

Aligning Manufacturers & Suppliers

Understanding the manufacturer's perspective

For legal manufacturers, the delivery of clean and biocompatible devices to the market is expected from the authorities (and patients).

Quality agreements | Clear quality agreements between legal manufacturers and suppliers are crucial to manage expectations and to align priorities and requirements.

Product quality | Manufacturers must monitor product quality, so it is essential to obtain continuous information regarding the ongoing processes at their suppliers' plants. Therefore, a cleanliness concept from a supplier is vital to prove the biological safety of the products throughout the entire process. Considering cleanliness aspects during all processes helps to decrease the risk of detecting unexpected substances in the chemical characterization tests performed on the final finished (ready to use) product according to ISO 10993-18. The interpretation of the results is facilitated when potential sources of contamination have previously been identified. Should unidentified substances be detected, further evaluation must be performed, and additional testing might be considered. This might extend project timelines, incur higher costs, and ultimately delay time to market and product access for the patient.

Process optimisation | After the successful submission or certification of the product, any change to the manufacturing must be assessed regarding the potential impact on biocompatibility. Therefore, manufacturers must collaborate with their suppliers to optimise manufacturing processes. With a concise process overview and knowledge on potential affected limit values, the evaluation of a process change is easier and may allow a risk-assessment with a limited selection of tests - or even no testing at all.

Aligning Manufacturers & Suppliers

Understanding the supplier's perspective

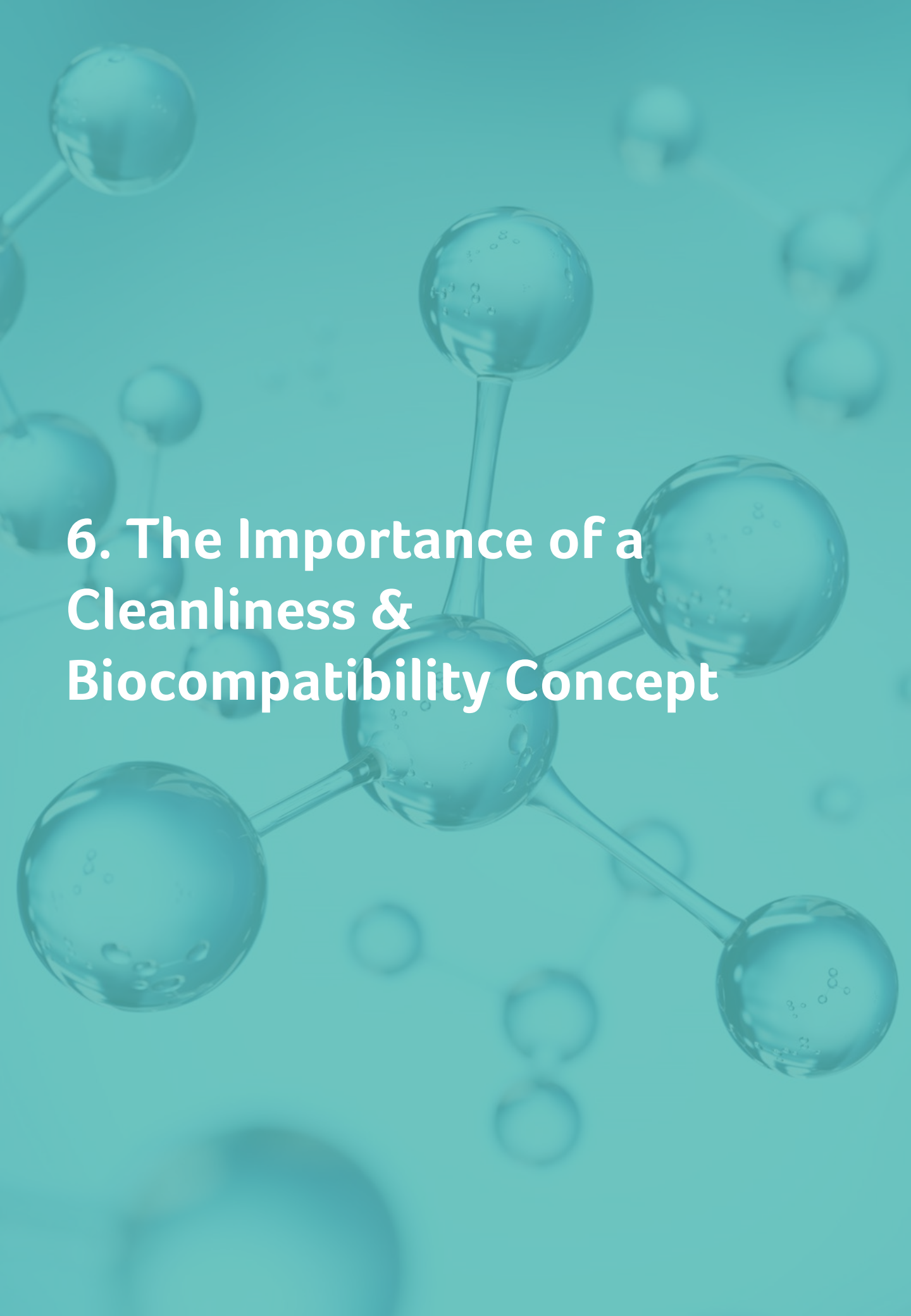
For suppliers, the delivery of clean products with a validated and monitored cleanliness concept is expected from a legal manufacturer (supplier's customer).

To be able to sell to different players in the medical device industry, many suppliers must meet broad requirements. And with no defined test programs and limit values in standards regarding cleanliness, each customer will likely have different expectations defined in their quality agreement.

Often there is a lack of knowledge to negotiate the adequate cleanliness requirements for the products to be delivered. As such, it is better to understand what the customer needs and **elaborate a specification as a proposal**.

Frequently, the delivered products are semi-finished and will undergo further processing in manufacturing. That means, that in some cases not all potential contamination categories contact the semi-finished product. With unknowns about the potential categories of contaminants and analytical tests required, and without limit values adapted to the specific material, geometry, or process outlined in the standards, suppliers should **avoid committing to specifications with their customers that cannot necessarily be fulfilled**.

Instead, ongoing honesty, communication, and collaboration to tackle the evolving situation should be favored.



6. The Importance of a Cleanliness & Biocompatibility Concept

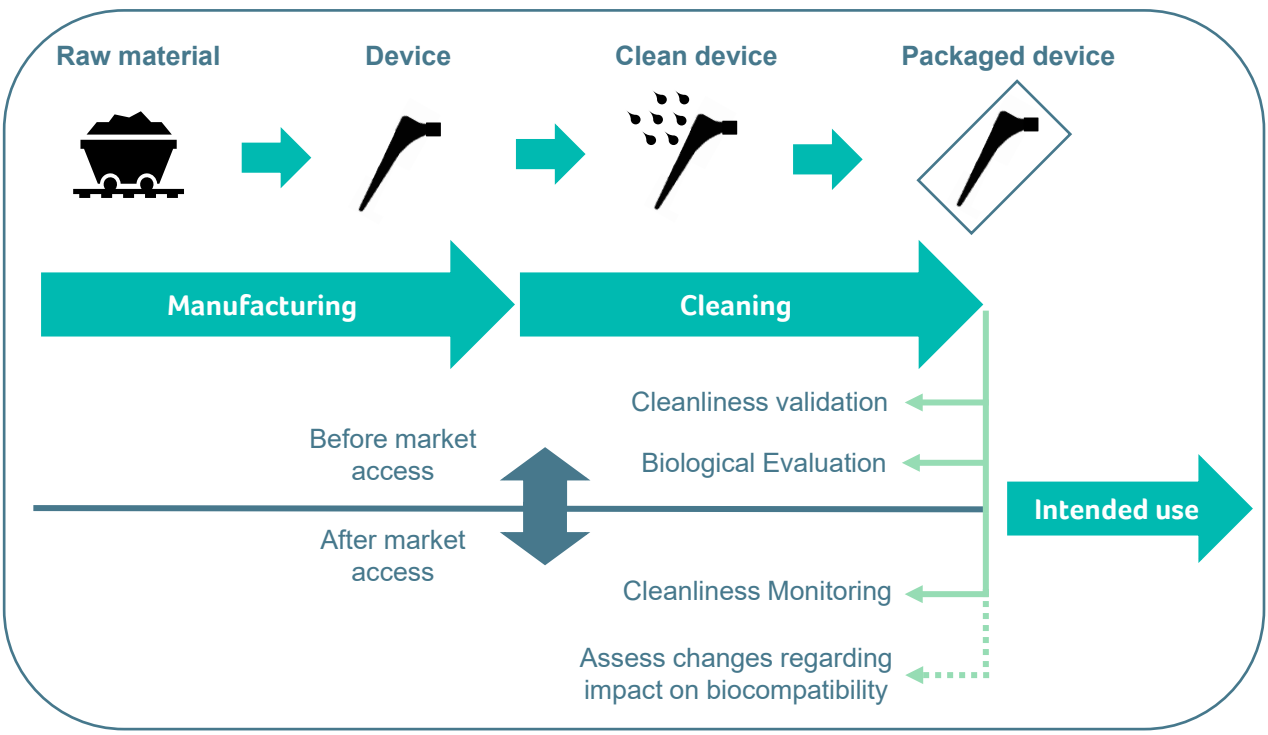
The Importance of a Cleanliness & Biocompatibility Concept

The biological evaluation is performed to prepare the documentation for the submission of a medical device based on the status quo. However, following the submission, it relies on the stability of the manufacturing processes - and in particular the final cleaning operation, demonstrating the importance of a cleanliness concept - and that any further modifications require being assessed. In theory, if the manufacturing process remains unchanged, no potential impact on cleanliness or in turn biocompatibility would be expected. This demonstrates why all stages of the manufacturing process must be controlled and all changes to processing steps must be evaluated.

The simplified visualization below shows the connection between biological evaluation (in particular the chemical characterization) and the cleanliness validation and monitoring.

Primarily, the idea of cleaning validation and monitoring is to show the continuous process quality. However, a stable manufacturing process and knowledge on potential contaminants from those operations are an important input for chemical characterization and facilitate the initial assessment and further change assessments.

To ensure the meaningfulness of information and data collected with cleaning validation and monitoring, the minimum requirements for the chemical characterization according to ISO 10993-18 should be known. Data that could be relevant including information about potential changes in the expected chemical characterization tests must be observed.



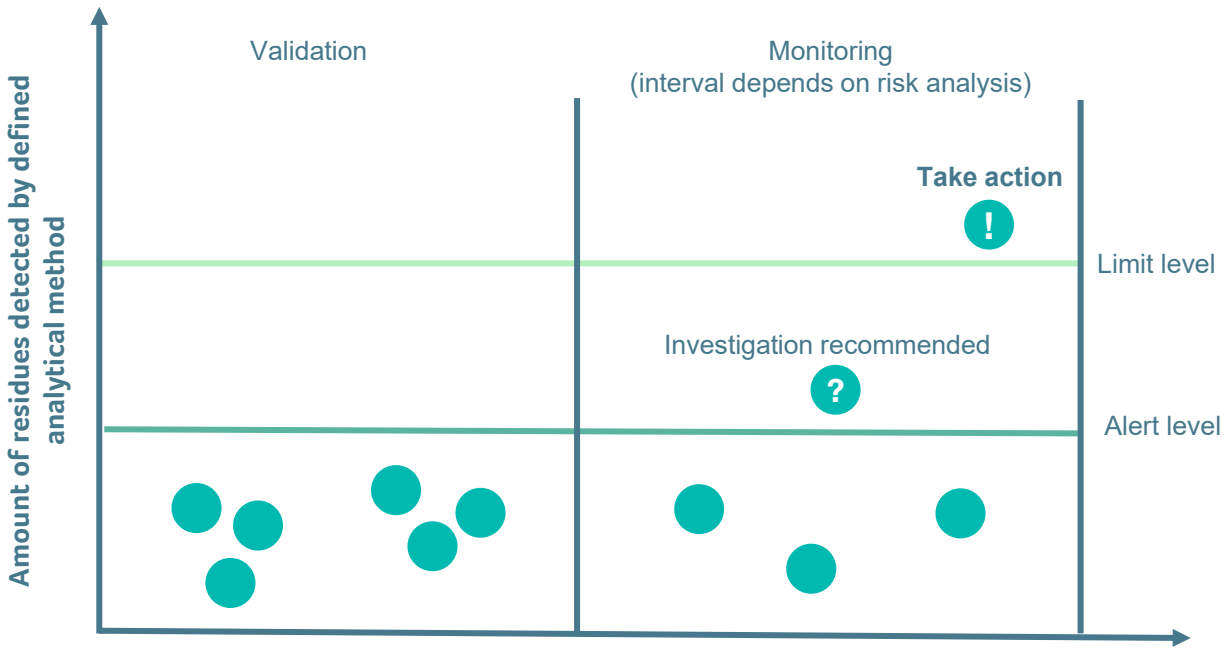
The Importance of a Cleanliness & Biocompatibility Concept

Adapted cleanliness concept

Cleaning validation is performed by selecting adequate methods to capture potential contaminations. After the validation process, the monitoring process must be introduced. Monitoring must be performed to ensure continuous process stability. For the monitoring, an alert level should be set in addition to the limit level. The alert level warns of a possible drift of the set operating conditions. When this level is exceeded, root cause analysis shall be performed which might include additional identification methods (as per ISO 10993-18) to interpret the higher values.

If the higher values cannot be traced to already-evaluated processing aids or material components, a toxicological and / or additional investigation shall be considered. The combination of the cleanliness concept with the characterizing methods can help to minimise the investigation effort.

If the monitoring results show a constant cleanliness level and no changes in production processes occur, the potential impact on biocompatibility is much lower. The collected results of the cleanliness can be implemented in the biological evaluation if the applied analytical methods are aligned with the chemical characterization procedure according to ISO 10993-18.



Analytical methods that can determine the amount of a substance and characterize it, can be used for further investigation (e.g., route cause analysis). Therefore, the results can be compared to the data from the chemical characterization studies used for the biological evaluation. In case equivalent substances were detected and toxicologically assessed, interpretation is facilitated.

The Importance of a Cleanliness & Biocompatibility Concept

How to set your specifications

Specifications highly depend on the material, process phase (process steps before and after), and the intended use of the medical device. As such, a risk-based approach according to ISO 19227 and ISO 10993-1 must be applied. Let's look at the main areas that impact the specification and risk for a medical device.

Firstly, a distinction must be made between the acceptable values for biological safety and cleanliness. Biosafety is about determining whether substances present on or in the device have an impact on biocompatibility due to their toxicity. Since each compound has its own toxicity profile, it is not feasible to establish specific limits, but an assessment can be undertaken to detect and quantify the compounds before a toxicological risk assessment is performed, to investigate potential risks.

Notably, before testing is performed, it is still required to set an appropriate analytical threshold (AET), which allows the detection of substances that might be toxicologically relevant.

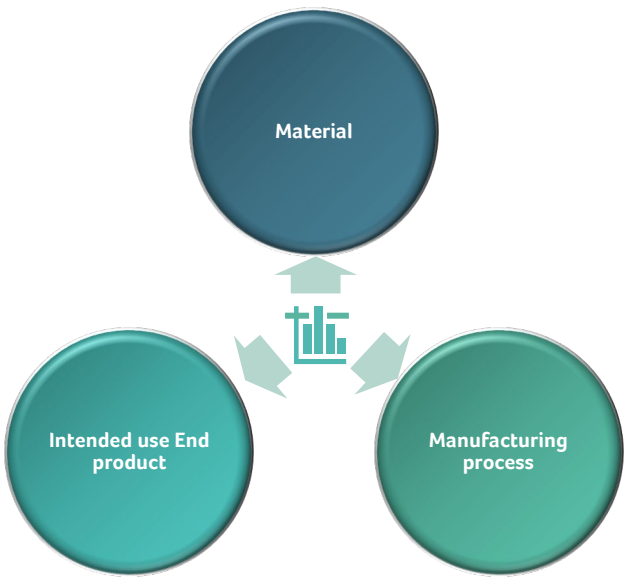
Cleanliness limits are about monitoring the manufacturing process to ensure the quality of products on an ongoing basis. Here it is important that the cleanliness criteria are chosen in such a way that possible trends potentially impacting biocompatibility are detected.

It is important to note that setting limits needs a thorough assessment and a comprehensible justification. The definition of limits needs a well-considered strategy, so we recommend involving experts like laboratory and validation specialists as well as toxicologists.

The Importance of a Cleanliness & Biocompatibility Concept

Depending on the material, the feasibility of the physical / chemical test must be approved.

It is usually easy to understand that the intended use and the process steps have an influence on the specifications. The fact that the material properties should be considered however, is usually overlooked. Since polymers can release increased quantities of components during analysis, this can overload the analyzers and make the corresponding trace analysis impossible. In this case, particularly if an incompatible solvent is used, that faces the technical limits of state-of-the-art analytics. The formation of worst-case families is possible and makes it easier to define limit values. With such a risk-based approach, the communication and discussion with other stakeholders such as suppliers, notified bodies, or customers is much easier.



Depending on the intended use, the cleanliness concept including defined criteria must be adapted to the corresponding risk.

Since we are discussing risk aspects, the risk in the intended use of the final product must be considered. With regards to limit values and criteria, aspects such as duration / type of body contact and contact surface have an influence on the risk assessment. As an example, the criteria for products with short-term contact (e.g., screwdrivers) might not be appropriate for a product with long-term contact (e.g., hip implants) due to the different criticality level. This recommendation also aligns with the risk assessment performed as part of the biological evaluation.

Depending on the process, the limit values should be set to ensure the feasibility of the next processing step.

Due to the complex manufacturing processes in medical technology, in which suppliers (i.e., outsourced processes) are often involved, it is important to identify the critical processes and evaluate them regarding cleanliness criteria in the risk assessment. That facilitates the definition of critical in-process cleaning steps with the corresponding criteria. If the necessary criteria are not met, it can lead to errors in downstream processes, affecting the cleanliness of the final product and in turn the safety of the medical device.

7. Summary

Summary

To ensure the biocompatibility of a medical device, a biological evaluation according to the ISO 10993-1 series is required, in which the cleanliness aspect plays a crucial role.

Due to the complexity of the MedTech industry, in-house data expertise and the creation of a cleanliness and biocompatibility concept are fundamental. The collection and monitoring of physical / chemical and microbiological data facilitates this derivation and reasoning.

Manufacturers and suppliers should strive for honest, ongoing communication to achieve the best outcomes. Producing clear quality agreements and working together to continuously optimise processes and product quality is key. Whilst manufacturers should aim for clarity in expectations and transparency of information, suppliers should avoid over-committing to specifications, and instead seek to understand what the customer needs and elaborate specifications as proposals.

In conclusion, whilst cleanliness relates to process-oriented key figures and biocompatibility relates to product-specific risk assessment, the concepts should be considered as intertwined rather than in isolation. Both are critical components of comprehensive quality assurance processes that facilitate the delivery of safe and effective medical devices to patients.

8. Standards & Guidances

Standards & Guidances

Below you'll find a list of helpful standards and guidances related to cleanliness and biological evaluation.

Standards

ISO 10993-1:2018 | Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process specifies the general principles, categorization, evaluation, and assessment of the biological safety of medical devices within a risk management process.

ISO 10993-17:2023 | Biological evaluation of medical devices Part 17: Toxicological risk assessment of medical device constituents specifies the process and requirements for the toxicological risk assessment of medical device constituents. The methods and criteria used to assess whether exposure to a constituent is without appreciable harm are also specified. The toxicological risk assessment can be part of the biological evaluation of the final product, as described in ISO 10993-1.

ISO 10993-18:2020/Amd 1:2022 | Biological evaluation of medical devices Part 18: Chemical characterization of medical device materials within a risk management process specifies a framework for the identification, and if necessary, quantification of constituents of a medical device, allowing the identification of biological hazards and the estimation and control of biological risks from material constituents, using a generally stepwise approach to the chemical characterization.

ISO 19227:2018 | Implants for surgery, Cleanliness of orthopedic implants, General requirements specifies requirements for the cleanliness of orthopaedic implants, and test methods for the cleaning process validation and controls, which are based on a risk management process.

ASTM E3418-23 | Standard Practice for Calculating Scientifically Justifiable Limits of Residues for Cleaning of Pharmaceutical and Medical Device Manufacturing Equipment and for Medical Devices provides procedures for calculating safe and scientifically justifiable limits of residues for use in cleaning validation studies of pharmaceutical / biopharmaceutical / medical device manufacturing equipment surfaces and medical device surfaces.

ISO/TS 21726:2019 | Biological evaluation of medical devices, Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents describes the basis for, selection of, and general applicability of a threshold of toxicological concern (TTC) value for a constituent present in / on a medical device or released from a medical device.

Standards & Guidances

Guidances

M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (2023)

This guidance emphasises considerations of both safety and quality risk management in establishing levels of mutagenic impurities that are expected to pose negligible carcinogenic risk. It outlines recommendations for assessment and control of mutagenic impurities that reside or are reasonably expected to reside in a final drug substance or product, taking into consideration the intended conditions of human use.

ICH guideline Q3D (R2) on elemental impurities - Step 5 (2022)

This guideline presents a process to assess and control elemental impurities in the drug product using the principles of risk management as described in ICH Q9. This process provides a platform for developing a risk-based control strategy to limit elemental impurities in the drug product. Whilst our whitepaper relates to medical devices, the approaches for impurities from pharmaceuticals are helpful in approaching the order of magnitude of limit values. The values cannot however be applied directly to medical devices.

Use of International Standard ISO 10993-1, “Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process” (2023)

The purpose of this guidance is to provide further clarification and updated information on the use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" to support applications to the FDA.

Congenius

Should you have a challenge related to Biocompatibility & Cleanliness, please do get in touch – our Operations team is ready and happy to help.

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