Regulatory surrounding (Biocompatibility)

Ensinger

- Test standards
- Regulations for medical devices
- Test details
- Testing on shapes

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Test standards

Regulatory surrounding (Biocompatibility)
Test standards

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ISO 10993

→ ISO is the International Standard Organisation

→ Biological evaluation of medical products

→ Define test procedures for biological and toxicological testing

→ Define different classes of medical products according to contact duration and nature of body contact

→ Internationally accepted and widely used

Regulatory surrounding (Biocompatibility)
Test standards

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United States Pharmacopeia Convention (USP)

→ US based non-profit organisation

→ Originally for pharmaceutical packaging

→ Create standards and requirements on quality, purity and identity for medical and pharmaceutical products

→ Define biological tests for different classes of medical products (class I to VI)

→ Mainly used in the Americas

Regulatory surrounding (Biocompatibility)
Test standards

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Food and Drug Administration (FDA)

→ FDA has a mission to protect public health in the USA and control the safety and affectivity of human and animal drugs, biological products, medical products, food and radiation emitting devices

→ Supply positive list of raw materials and processing aids for use with direct food contact

→ Determine toxic limits per substance for long term migration into food stuff

→ Indication and support for medical applications, but no direct transfer into biocompatibility testing!

Regulatory surrounding (Biocompatibility)

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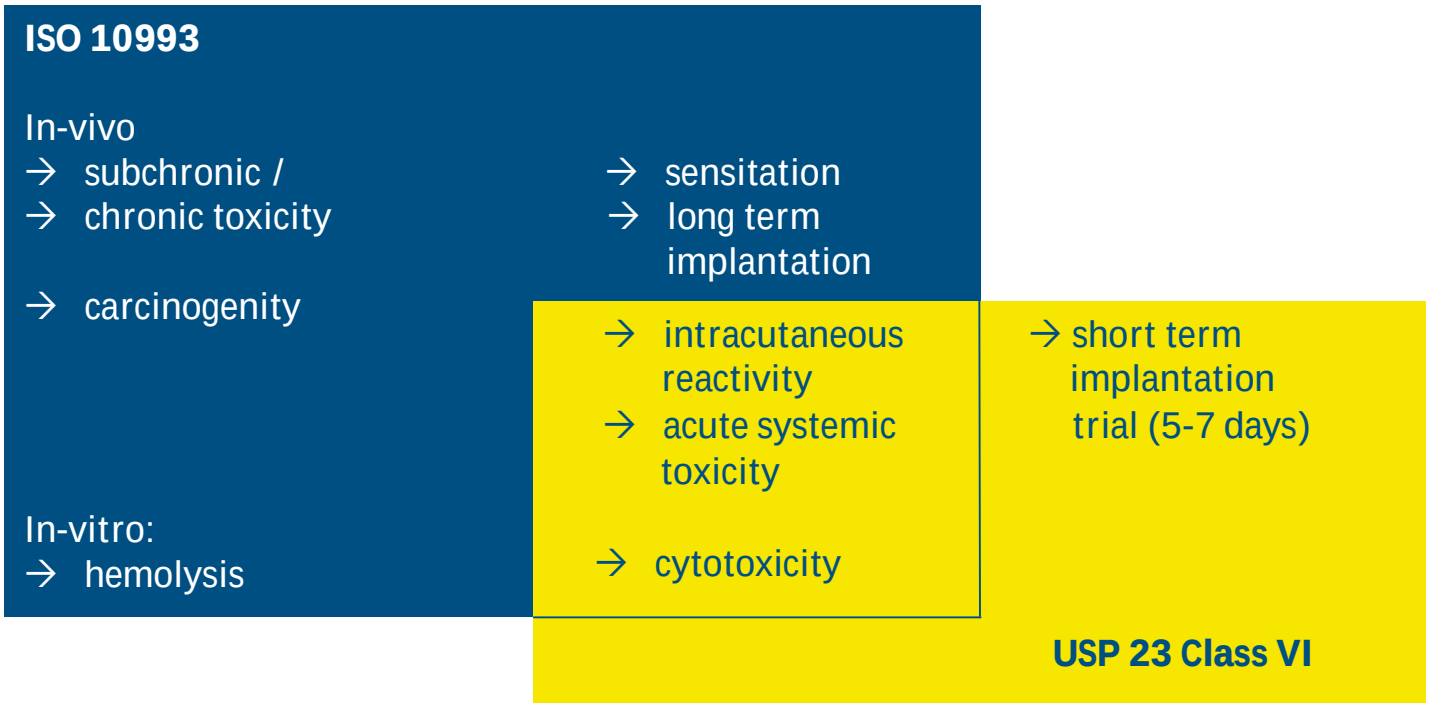
Comparison on biocompatibility testing



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Regulations for medical devices

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Regulations for medical devices

→ Given the current medical products laws, the marketer of the medical device has to bring a proof of physiological safety on the final device and do this in the final stage testing on biocompatibility.

→ The tests have to consider:

- → geometry and surface of the final device
- → pre-treatment of the surface (grinding, cleaning, sterilisation, ...)
- → post-curing (e.g. ageing after hot steam sterilisation)

to evaluate the biological consequences in the intended use.

→ Biological safety on the final device can be proven by:

- → biological /clinical testing
- → toxicological evaluation if already given clearance for a similar product
- → chemical testing

Regulatory surrounding (Biocompatibility)
Regulations for medical devices

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Customer requests

→ Risk assessment for material selection:
Early indication if time and money for final clinical testing is invested properly.

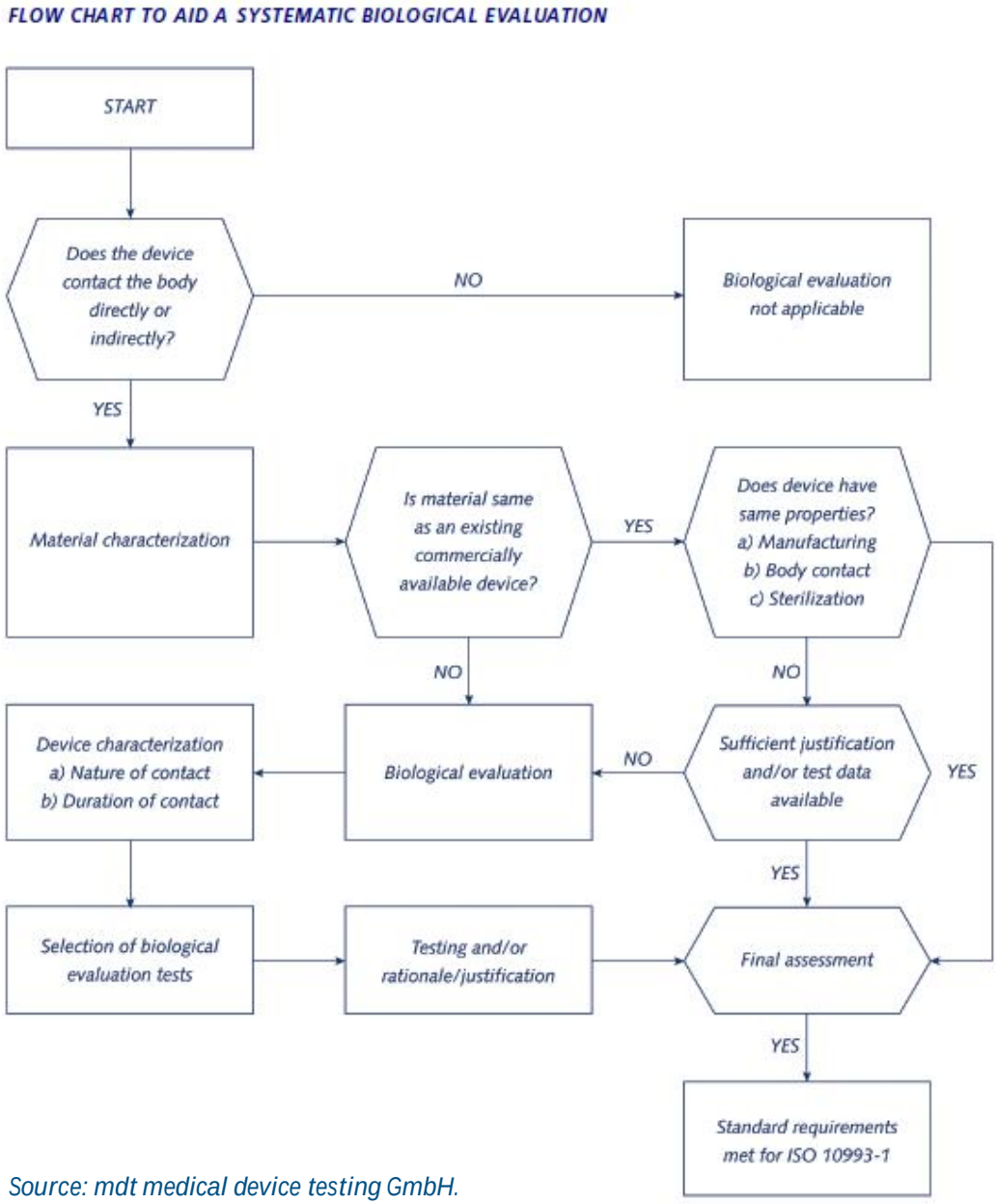
→ Pre-qualification:
To choose material that will pass the testing anyway and has been already qualified as suitable for use in the intended application.

→ Material characteristics:
A plastic or its degradation products should not give-off toxic products or provoke an allergic reaction in the human body when used in a medical product.

→ Support in approval process:
Statements and documentation for submission to authorities qualifying the material used

Regulatory surrounding (Biocompatibility)

Biological safety evaluation scheme for medical devices given in ISO 10993:



Source: mdt medical device testing GmbH. Performance Safety Compliance, V6, 2009

Regulatory surrounding (Biocompatibility)

Biological safety evaluation scheme for medical devices given in ISO 10993:

INITIAL AND SUPPLEMENTARY EVALUATION TESTS FOR CONSIDERATION

Medical Device Categorization			Biological Effect											
Nature of body contact		Contact duration A – limited ≤ 24 h B – prolonged 24 h - 30 days C – permanent > 30 days	Cytotoxicity	Sensitization	Irritation	Acute toxicity	Subchronic toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic toxicity	Carcinogenicity	Reproductive toxicity	Biodegradation
Surface device	Skin	A	x	x	x									
		B	x	x	x									
		C	x	x	x									
	Mucosal membrane	A	x	x	x									
		B	x	x	x	•	•		•					
		C	x	x	x	•	x	x	•		•			
	Breached or compromised surface	A	x	x	x	•								
		B	x	x	x	•	•		•					
		C	x	x	x	•	x	x	•		•			
External communicating device	Blood path indirect	A	x	x	x	x				x				
		B	x	x	x	x	•			x				
		C	x	x	•	x	x	x	•	x	x	x		
	Tissue, bone, dentin	A	x	x	x	•								
		B	x	x	x	x	x	x	x					
		C	x	x	x	x	x	x	x		x	x		
	Circulating blood	A	x	x	x	x		•		x				
		B	x	x	x	x	x	x	x	x				
		C	x	x	x	x	x	x	x	x	x	x		
Implant device	Tissue, bone	A	x	x	x	•								
		B	x	x	x	x	x	x	x					
		C	x	x	x	x	x	x	x		x	x		
	Blood	A	x	x	x	x	x		x	x				
		B	x	x	x	x	x	x	x	x				
		C	x	x	x	x	x	x	x	x	x	x		

x zu berücksichtigendes Risiko gemäß EN ISO 10993-1

• zusätzlich zu berücksichtigendes Risiko gemäß "Blue book memorandum G95-1"

x *to be considered in accordance with EN ISO 10993-1*

• *to be considered additionally for US registrations (Blue Book Memorandum G95-1)*

Source: mdt medical device testing GmbH. Performance Safety Compliance, V6, 2009

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Test details

Regulatory surrounding (Biocompatibility)
Test details

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Most common tests for medical devices in contact with blood and tissue for <24h:

→ In-vitro testing (test dish / tube):

- → Cytotoxicity ISO 10993-5
- → Hemolysis ISO 10993-4

→ In-vivo testing (animal):

- → Sensitization ISO 10993-10
- → Intracutaneous reactivity ISO 10993-10
- → Acute systemic toxicity ISO 10993-11
- → Subchronic systemic toxicity ISO 10993-11

→ Analytic testing:

- → Chemical analysis of soluble substances (ISO 10993-18)

Source: mdt medical device testing GmbH. Performance Safety Compliance, V6, 2009

Regulatory surrounding (Biocompatibility)
Test details

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Cytotoxicity (ISO 10993-5):

→ approved fundamental test for all medical devices to inform about inert biological behaviour

→ detect toxic and harmful substances that might migrate during intended use of a material

→ evaluates quantitative growth inhibition on cell cultures within the intended contact duration (24h, 30d) tested on mouse fibroblasts (in-vitro) with diluted extract of solubles

→ colorimetric determination of endpoint (growth inhibition)

Source: mdt medical device testing GmbH. Performance Safety Compliance, V6, 2009

Regulatory surrounding (Biocompatibility)
Test details

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Hemolysis (ISO 10993-4):

→ testing for toxic impact on human blood

→ tested on human erythrocytes (in-vitro) with diluted extract of solubles

→ control on abnormal behaviour or toxic reactions

Source: mdt medical device testing GmbH. Performance Safety Compliance, V6, 2009

Regulatory surrounding (Biocompatibility)
Test details

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Sensitization (ISO 10993-10):

→ evaluation of possible sensitizing properties as allergens act almost irrespectively of their dose

→ most commonly test used: maximization acc. to Magnusson und Kligman

→ tested in-vivo on 15 guinea pigs (10 treated + 5 control animals)

→ treated interdermally and dermally with material extracts at weekly intervals

→ control on dermal challenge, allergic reactions or abnormal behaviour

Source: mdt medical device testing GmbH. Performance Safety Compliance, V6, 2009

Regulatory surrounding (Biocompatibility)
Test details

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Irritation (ISO 10993-10):

→ evaluation of potential inflammatory reactions after single or multiple application of a material extract for local irritation

→ 3 common test procedures:

- → dermal (on the skin)
- → ocular (in the eye)
- → intracutaneous reactivity (in the skin)

→ 3 rabbits per test procedure

→ single application of material extract and 72h observation period

→ control on local irrication reactions

Source: mdt medical device testing GmbH. Performance Safety Compliance, V6, 2009

Regulatory surrounding (Biocompatibility)
Test details

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Systemic toxicity (ISO 10993-11):

→ evaluation of risk for systemic toxic reactions caused by toxic substances available in the human body over a long period of time

→ 3 common test procedures:

- → acute (<24h)
- → subchronic (>24h up to 10% of the life span of the test individual)
- → chronic (>10% of the life span of the test individual)

→ oral, intravenous or intraperitoneal application of extracts

→ 3 male + 3 female rats (acute systemic toxicity)
10 male + 10 female rats (subchronic systemic toxicity)

→ daily observation over 14 resp. 28 days + final histopathological evaluation

Source: mdt medical device testing GmbH. Performance Safety Compliance, V6, 2009

Regulatory surrounding (Biocompatibility)
Test details

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Chemical analysis of soluble substances / „GC/MS-Fingerprint“ (ISO 10993-18):
(Characterization of extractable organic substances in polymeric materials)

→ extraction with 3 aquaeous and/or organic solvents in accordance with EN ISO 10993-12

→ system standardization with external reference compound

→ identification of typical extracted substances using a mass selevtive detector

→ semi quantitative evaluation by GC-MS (gas chromatography with mass selective detector)

→ allows preparation of a toxicological profile

→ biological evaluation of the results, comparison with experience data and final risk assessment

Source: mdt medical device testing GmbH. Performance Safety Compliance, V6, 2009

Regulatory surrounding (Biocompatibility)

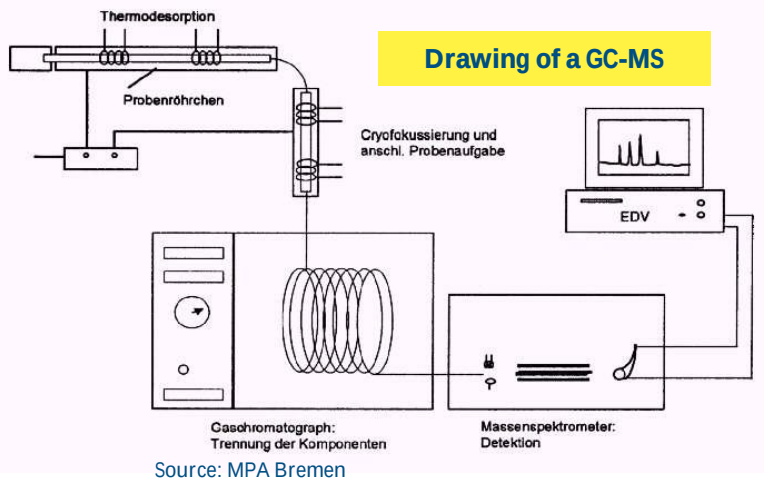
Test details

Analytical method for ISO 10993-18
GC-MS (gas chromatography with mass selective detector)

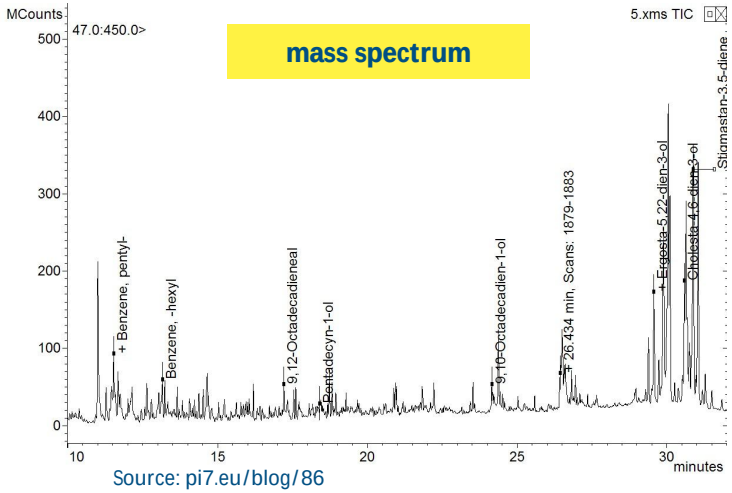
= coupling of a gas-chromatograph (GC) with a mass selective detector (MS) :

→ the gas chromatograph is used to separate the substances in the sample that should be analysed

→ the mass selective detector is used to identify the substances and if possible even quantifies the ratio per component



Source: MPA Bremen



Source: pi7.eu/blog/86

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Testing on shapes

Regulatory surrounding (Biocompatibility)
Testing on shapes

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→ Stock shapes are no medical devices because they are not finalised in their form, surface and processing – they are semi-finished products!

→ No testing on stock shapes is mandatory according to any law

→ There is no valid norm for testing biocompatibility on semi-finished products

→ Test matrix for medical products can be taken as guideline for stock shape testing

→ Testing on stock shapes can only be an indication / material characteristic because of the influence of following processing steps (cooling agent, cleaning)

Regulatory surrounding (Biocompatibility)
Testing on shapes

Ensinger

Discussions with biocompatibility testing labs gave the following recommendation:

→ Tests on stock shapes are only material specific indication to inform about general suitability for medical devices, they DO NOT free final marketers from testing on the final device!
Although it might be possible in individual cases to transfer the result from one test to another. This can only be done within the same manufacturing process at the OEM and doesn‘t have to be necessarily in-vivo tested but can also be a general chemical characterisation!

→ ISO 10993-1 (valid since 2010) focuses on the evaluation of the test substance via chemical characterisation (analysis of migrating substances and their risk assessment for biological effects). Only if there is any indication on possible issues with the material, animal tests are considered as prove! There must always be a reason and explanatory statement for the animal testing.
This stepwise approach acc. to ISO 10993-1 is mandatory and also mentioned in each single paragraph (e.g. -10)!

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Biocompatibility

Status Ensinger

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How is Ensinger supporting its customers?

Ensinger is testing all stock items, suitable for medical applications with a combined testing according to ISO 10993.

Ensinger‘s target is:

→ To offer a most extensive basis possible for the material evaluation and risk assessment in a very early stage of the development process of a medical device

→ To support our customers in choosing pre-qualified stock shapes by reasonable tests and certificates for stock shapes

→ To support our customers to reduce the risks during clinical trial stage in advance

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What exactly is Ensinger testing?

Ensinger is testing the suitable stock shapes for medical applications with a combined testing of:

→ ISO 10993-5 (Cytotoxicity)
→ ISO 10993-4 (Hemocompatibility)
→ ISO 10993-18 (Chemical Analysis / Fingerprint)
→ ISO 10993-1 (Biological-toxicological assessment of the results)

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Why is Ensinger not directly testing according to ISO 10993-10 and ISO 10993-11?

In line with the norm update in 2010, the chemical analysis according ISO 10993-18 was added which prescribes, that only in case of a concrete suspision a step-by-step approach for in-vivo tests (animal testing) according ISO 10993-10 and -11 should be carried out. Ensinger is therefore following the new updated norm.

ISO 10993-18 even gives more accurate and broader information for material qualification than ISO 10993-10 and -11.

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Why doing a material characterisation according to ISO 10993-18?

→ Support of risk management in evaluating the biological overall safety for a medical product based on the material characteristic

→ Identification and where applicable quantification of all extractable sustances, to evaluate in advance the toxicological risk of the material in use

→ Evaluation of equivalency of new material grades with clinically proven materials

→ Evaluation of the equivalency of a final valid medical product with the in advanced tested prototypes or materials

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What are the advantages of the approach according to ISO 10993-18?

1) The chemical analysis provides highly accurate results, driven by the technical progress in this field. Not only the symptoms of the extracted, dissolved substances are observed but also identified and therefore detected as initiator of the symptom.

2) Very low detection limits (in the ppm range) are possible.

3) For the chemical analysis aggressive solvents can be used to dissolve potential critical and therefore more substances, than could be used in animal testings.

4) Distortion of results can be eliminated by analytical methods which could be caused in in-vivo tests by the immune reaction of the animal.

5) Unnecessary animal testings at guinea pig, mouses, rats and rabbits can be avoided.

6) In addition to the Fingerprint testings (ISO 10993-18), the testing on cytotoxicity (ISO 10993-5) and hemolysis (ISO 10993-4) ensures, that products have **sufficient inert** properties compared to tissue and blood and a defined toxicological profile.

Biocompatibility – Status Ensinger

For which MT materials Ensinger can order-related confirm the biocompatibility according to ISO 10993?

→ For all standard stock items of the MT portfolio, Ensinger is able to confirm the tested biocompatibility according to ISO 10993-1, -4, -5 and -18

→ Furthermore test on biocompatibility on the raw material are listed, if provided by the raw material manufacturer

→ For non-stock items of our MT portfolio, Ensinger is able to offer customer-related test, nevertheless no standard testings are undertaken

Thank you very much for your attention