The FAIR Premium Implant-System ICX

Quality and Biocompatibility Safety Assessment of the ICX-templant®

medentis medical

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Medical Device companies manufacturing and marketing their products in the global market must adhere to very strict quality and process controls, and must have systems and controls in place to satisfy global regulatory requirements, standards and directives. Medentis ICX-templant implant products, processes and services comply dental implants with ISO 9001: 2008 - quality management system, ISO 13485:2012 quality management system for medical devices and Medical Device Directive 93/42 EEC:1993. All medentis products are marked with batch numbers and all raw materials at the OEM manufacturer are monitored regularly. All products are subject to strict quality control at all stages of production at the OEM manufacturer and at delivery at medentis. ICX-templant Implants undergo a very severe sterilization procedure – exposure to gamma rays, in accordance with the requirements of European laws and directives. The medentis quality management team consists of an experienced and highly qualified staff who conduct internal and external audits. Internal audits closely examine the various stages of product development while external audits inspect our processes and suppliers. Quality management is process-oriented, and quality assurance acts on a future-oriented basis. medentis controls the quality of its products for consistency and sustainability using tests conducted at the medentis medical evidence center with state of the art technical equipment. Quality tests are performed throughout the entire manufacturing process:

1. Biological safety assessment according to DIN EN ISO 10993
2. Assessment of bioburden according to DIN EN ISO 11737-1 and endotoxin levels according to the pharmacopeia (Ph. Eur. 6, 2.6.14)
3. Dynamic fatigue test for endosseus dental implants accordng to ISO 14801:2007 and corrision test to DIN Norm EN ISO 13927
4. XPS (X-ray Photoelectron Spectroscopy) und EDX (Energy Dispersive X-Ray Fluorescence) analysis to monitor and ensure surface cleanliness
5. Microgap analysis
6. Check of Manufacturing-related and process-related tolerances
7. Regular supplier audits
8. Internal quality check with batch release
9. Regular exchange with expert circles and University institutes for a direct reflection of feedback

Medentis maintains key relationships with universities, publications, and renowned clinicians in nearly all key market segments including general dentistry, periodontics, oral and maxillofacial surgery, prosthodontics, and dental laboratories. Medentis distributes a majority of implants and prosthetic components, with sterility and biocompatibility verifications being performed for each product family. Every implant undergoes a rigorous and detailed visual inspection, assuring greater quality control. At medentis, ongoing improvement of our products and services for the purposes of enhancing patient care and increasing the effectiveness of your individual practice is a promise we stand by. By consistently improving and expanding the ICX product line, medentis has earned a reputation as an innovator of trend-setting products, technology, and techniques in implant dentistry. This position ensures customers to be confident that our products will perform and deliver under the most demanding clinical circumstances.
In the sections below we will refer to bulletin 1-3. Detailed information to bulletin 3-9 will be given in our corresponding folders.

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Biocompatibility

Submissions for approval and launching of medical devices by regulatory authorities require that quality and biocompatibility assessment be conducted to assure safety of the device or material. Safety data can be obtained by testing according to certain prescribed or recommended guidelines, including guidance documents developed by the International Organization for Standardization (ISO). These guidelines include e.g. ISO 10993, „Biological Evaluation of Medical Devices". The categorization of medical devices based on type and duration of contact specifies the areas of biocompatibility that should be investigated (Table 1).

Tab. 1. Initial Evaluation Tests for Consideration (ISO 10993-1: Biological Evaluation of Medical Devices Part 1, Attachment A, 2013)

Classification		**Biological Effects**							
Body contact	Contact period (> 30 Days)	Cytotoxicity	Sensitization	Irritation oder intrakutane Reaktivität	Systemic Toxiciity (acute)	Subchronic Toxicity (Subakucute)	Gentotoxicity	Implantation	Hämokompatibiliity
Tissue/ Bone		X	X	X	X	X	X	X	
Blood		X	X	X	X	X	X	X	X

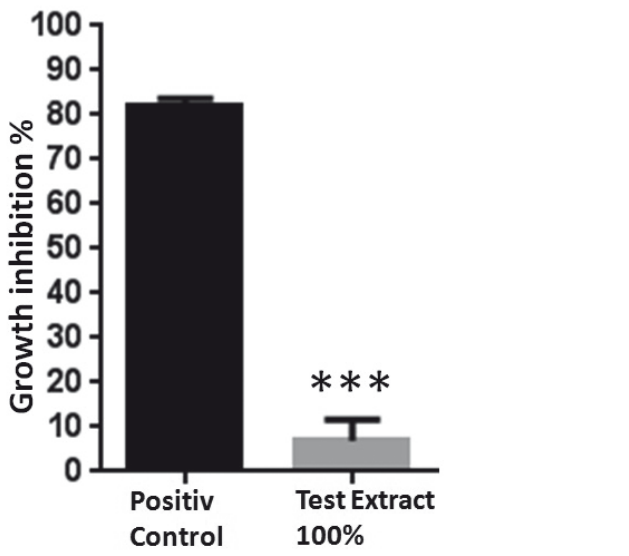
During the CFDA (China Food & Drug Administration) submission process of the ICX-templant system a couple of tests based on ISO Norms 10993-3, 4, 5,6,10 and 11 were performed at the Sichuan Testing Center for Biomaterials and Medical Devices. All test results confirmed the overall reliable biocompatibility of tested ICX-templant specimen. As a part of a regularly quality control cytotoxicity (10993-5), genotoxicity (10993-3) and Extractables & Leachable (10993-18) tests were performed in accredited „states of the art laboratories on behalf of medentis (fig.1 and 2).

Cytotoxicity according to ISO 10993-5

The in vitro tests for cytotoxicity assess the response of cells in culture to direct contact with devices or to their extracts. ISO 10993-5 (1999): „Tests for In Vitro Cytotoxicity" specifies procedures for testing devices by direct or indirect contact, extracts of devices, and filter diffusion. Extracts of test devices and materials are tested by exposure to the cell culture system (e.g. L929 mouse fibroblast cell line). The growth inhibition test is performed according to the requirements described in Biological evaluation of medical devices – Part 5: Tests for in vitro cytotoxicity. The test article, positive and negative controls are extracted according to the method ISO 10993-12. The original extract is serially diluted and 5 concentrations are used for testing. L-929 cells are treated with extracts of the sample, reagent control, negative control or positive control. Triplicate plates are prepared for each treatment. The cells are incubated for at least 24 hours and observed microscopically for cytotoxic effects.

Figure 1 Growth inhibition test (n=10). Cell monolayers are grown to near confluence in flasks and are then exposed to test items (ICX templant implants) indirectly by means of fluid extracts. Extracts are obtained by placing the test and control items in separate cell culture media under standard conditions according to ISO 10993-5. Each fluid extract obtained is then applied to a cultured-cell monolayer, replacing the medium that had nourished the cells to that point. In this way, test cells are supplied with a fresh nutrient medium containing extractables derived from the test item or control. The cultures are then returned to the 37°C incubator and periodically removed. The proliferation of cells was determined quantitatively via colorimetric reaction with an ELISA plate reader. Statistics were performed with an One-Way ANOVA Test (Graph Pad Prism 6.0). (Data derived by BSL Bioserv; Tests performed (2014) by BSL Bioserv, Planegg, Germany Studydirector Dr. Dipl. Biol. Christian Hoy, all original data at medentis medical GmbH).

(Fig.1)

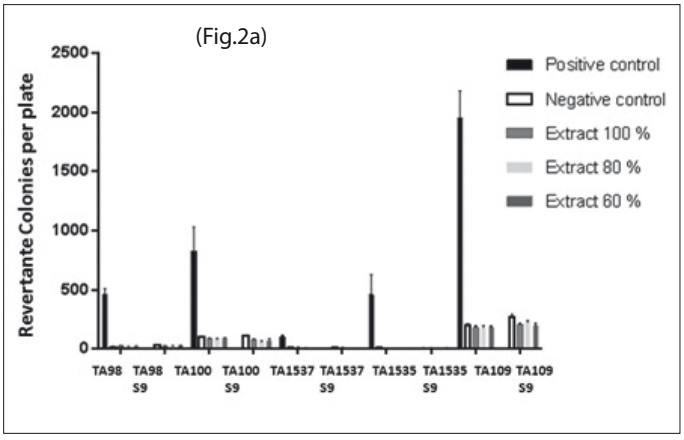


*** p < 0.001 positive control vs. Test Extract
n= 10 independent experiments (each in triplicates)

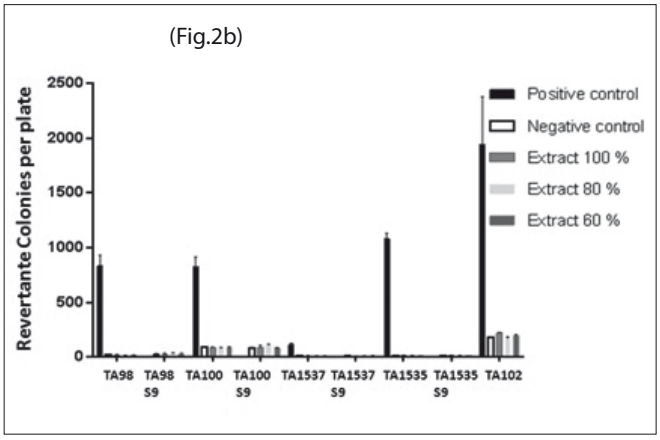
Genotoxicity with the Reverse Mutation Test (AMES) according to ISO 10993-5

ISO 10993-3, „Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity," recommends that the potential for genetic toxicity be assessed using a series of at least three assays. Two of these assays should use mammalian cells as the test system, and the tests should cover the three levels of genotoxic effects: DNA effects, gene mutations, and chromosomal aberrations. The International Conference on Harmonization (ICH) „Guidelines on Genotoxicity: A „Standard Battery" for Genotoxicity Testing of Pharmaceuticals, „are currently being applied to medical device assessments as well. These guidelines recommend a three-test battery. These tests include reverse mutation assay using Salmonella typhimurium and Escherichia coli strains of bacteria, the AMES assay (Fig.2), the in vitro chromosomal aberration assay or the mouse lymphoma tk+/- mutation assay, and the in vivo rodent bone-marrow micronucleus assay. The principle of the test based on strains of Salmonella that are unable to synthesize histidine are introduced into a test substance lacking in histidine. If the strains then regain the ability to synthesize histidine, the substance is considered mutagenic and thus carcinogenic (Figure 2).

(Fig.2a)



(Fig.2b)



2. Bioburden test

Bioburden is normally defined as the number of bacteria living on a surface that has not been sterilized. The term is most often used in the context of bioburden testing, also known as microbial limit testing, which is performed on pharmaceutical products and medical products for quality control purposes. Products or components used in the pharmaceutical or medical field require control of microbial levels during processing and handling. Bioburden or microbial limit testing on these products proves that these requirements have been met. Bioburden testing for medical devices made or used in the USA is governed by Title 21 of the Code of Federal Regulations and worldwide by ISO 11737:1. The aim of bioburden testing is to measure the total number of viable micro-organisms (total microbial count) on a medical device prior to its final sterilization before implantation or use. The bioburden has to be among the alert limit of >1 CFU/component.

3. USP Pyrogen test und Bacterial Endotoxin LAL test

Pyrogen is a substance that induces fever upon blood contact in mammals. Deriving, for instance, from fragments of Gram-negative or Gram-positive bacteria, pyrogens can occur even in sterilized products, and have the capacity to pose a serious health threat to patients receiving parenteral treatments. The presence of such pyrogens can be assessed with e.g. the in vitro Monocyte Activation Test (MAT), a validated testing system that constitutes a complete replacement of the rabbit pyrogen procedure for the quality control of injectables. It comprises six variants of the same principle: the fact that cells produce cytokines upon contact with fever-inducing substances, so-called pyrogens. This reaction is (within a certain range) dose-dependent, and permits a quantitative determination of pyrogenic contents. One prominent feature of the MAT is that, unlike the LAL, it is not restricted to endotoxins. Another test system, which exclusively detects endotoxins from Gram-negative bacteria, is the LAL (Limulus amoebocyte lysate) test. The reaction of the lysate with the endotoxin can be measured chromogenically, or by turbidity assessment. The USP limit of the endotoxin maximum is 20 EU/device (Ph. Eur. 6, 2.6.14).

Figure 2a, 2b The Ames test combines a bacterial revertant mutation assay with a simulation of mammalian metabolism to produce a highly sensitive test for mutagenic chemicals in the environment. A rat liver homogenate is prepared to produce a metabolically active extract (S9). The S. typhimurium bacteria strains are constructed to differentiate between base pair (TA100, und TA 1535 und TA 102) and frameshift (TA 1537, TA 98) mutations. The test item was extracted in a polar extraction and non-polar extraction medium according to ISO 10993-3, 2003 and ISO 10993-12. After extraction the polar and non polar extracts were centrifuged at room temperature for 5 minutes at 1000 g. Positive and negative controls were included in the experiment. Genotoxicity can be detected by a clearing or rather diminution of the background lawn or a reduction in the number of revertants down to a mutation factor of approximately < 0.5 in relation to the extract vehicle control. (Graph Ames test performed (2014) at BSL Bioserv, Planegg, Germany Studydirector Dipl. Biol. Anja Holz Original data at medentis).

Table 2: Testing of biocompatibility of the material Titan Grad 4 of the ICX Templant Implants according to DIN EN ISO 10993, OECD guidelines etc.

Biological risk	Norm/Guideline	Test	Resultat	Remarks
Cyotoxicity	EN ISO 10993-5, DIN EN ISO 1174, USP 30 <87>, AS 2696 App. C. BS 5736 Part 10	Growth inhibition Test [1]	Growth inhibition < 30%	
Genotoxicity	DIN EN ISO 10993-3, OECD 471	Reverse Mutation Test (Ames Test) [1,2,3]	Non genotoxic	Bacteria
	DIN EN ISO 10993-3, OECD 476	TK Gene Mutation (Mouse Lymphoma Assay) [3]	Non genotoxic	Mammalia
	DIN EN ISO 10993-3, OECD 473	Chromosom abberation test [3]	Non genotoxic	Mammalia
Toxicity	DIN EN ISO 10993-11 OECD 473	Acute Toxicity [3]	No acute toxicity	28 Days Study
	DIN EN ISO 10993-11 OECD 473	Subchronic Toxicity [3]	No subchronic or chronic Toxicity	90 Days Study
Skin Sensitization Test	DIN EN ISO 10993-10 OECD 406	Irritation or Intracutaneous reactivity [3]	No irritation and sensitization	
	DIN EN ISO 10993-10 OECD 406	hypersensitivity [3]	No irritation and sensitization	
Implantation	nach DIN EN ISO 10993-6	Subcutane Implantation [3]	No local effects after implantation	12 Week Study
	nach DIN EN ISO 10993-6	Bone Implantation [3]	No local effects after implantation	26 Week Study
Hemolysis	DIN EN ISO 10993-4	Hemolysis [3]	No hemolytic effect	
Pyrogen/Endotoxin Test	Ph. Eur. 6, 2.6.14 Ph. Eur. 6, 2.6.8	LAL, Pyrogen (MAT) [3]	negative	
Microbial load on medical products	DIN EN ISO 11737:1	Bioburden [4]	negative	
chemical compounds and inorganic elements that migrate from a material (Extractables) or from the product/ packaging/container (Leachables)	DIN EN ISO 10993-18	Extractables & Leachables [3]	negative	

1) Test performed (2014) by BSL Bioserv, Planegg, Germany Studydirector Dr. Dipl. Biol. Benjamin Hoy , 2) Test performed (2014) by BSL Bioserv, Planegg, Germany Studydirector Dipl. Biol.Anja Huber, 3) Test performed (2014) by Sichuan Testing Center for Biomaterials and Medical Devices, Sichuan, China Studydirector Biol. Jie Liang, 4) Test performed (2014) by Zwisler Laboratorien, Konstanz, Deutschland Studydirector Dr. Dipl. Biol. Christian Drainig, 5) Test performed (2014) by BSL Bioserv, Planegg, Deutschland Studydirector Dipl.Ing (FH) Ingrid Bierl

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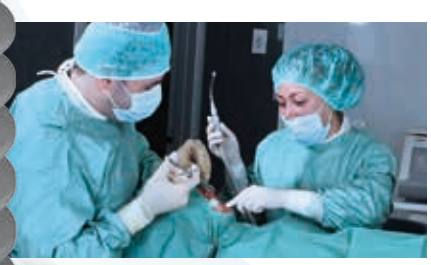

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