CleanControlling®
MEDICAL

TESTING MEDICAL PRODUCTS FOR SURFACE CONTAMINANTS

CleanControlling GmbH was founded in 2006 and is an independent, accredited testing laboratory. As a specialist for conducting cleanliness analyses, CleanControlling GmbH can draw on extensive experience in the field of technical cleanliness.

CleanControlling is actively involved in an industrial association and in drawing up standards for the revision of VDA19.

CleanControlling Medical GmbH & Co. KG was founded with a biological laboratory in 2014 in response to an increasing demand in the medical technology industry.

OUR STRENGTHS – YOUR ADVANTAGE

EXPERTISE

Qualified, competent testing personnel: Doctors in Biology / Biotechnology Bachelors / Biological Technical Assistants

- Comprehensive range of services: Everything from a single source
- Comprehensible reports in German and English (FDA-compliant)
- Personal support for the interpretation of results.
- At the heart of the "World Center of Medical Technology"
- Free pick-up service for test objects in the Tuttlingen area in Germany

ACCREDITATION

ilac-MRA

DAkkS Deutsche Akkreditierungsstelle D-PL-19887-01-00

good laboratory practice glpcompliance

Anerkannt durch/Recognized by Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten www.zlg.de

ZLG-AP-189.15.11

WHY AN ACCREDITED, GLP-APPROVED LABORATORY?

The accreditation confirms that the test laboratory complies with international normative quality and expertise requirements and that the test results are therefore internationally comparable and accepted. It provides objective proof of the quality and expertise of the work of a testing laboratory. Commissioning an accredited testing laboratory is also essential for validation and approval processes to ensure recognition of audit results.

Good Laboratory Practice (GLP) is a quality assurance system for laboratories which conduct non-clinical tests in the health and environmental sector. With GLP approval, tests conducted in accordance with the principles of the GLP can be mutually recognized by the regulatory authorities of the OECD member countries*, and test results can therefore also be accepted by the FDA.

* Europe, USA, Canada, Japan, Mexico, Australia and others

THE COMPANY

DIPL.-ING (M.ENG.) (FH)
VOLKER BURGER
CEO

Volker Burger founded CleanControlling GmbH in 2006 due to his particular fascination for the topic of "technical cleanliness". Prior to that, during his time as manager of the Process and Product Development department at an automotive supplier, he was repeatedly confronted with the issues and challenges of technical cleanliness. Based on these experiences CleanControlling GmbH developed into one of the leading specialists in the field of technical cleanliness, with profound knowledge from over 12 years of laboratory analysis, consulting and training. Quality and reliability are the two most important cornerstones of the company's philosophy.

Since founding the CleanControlling GmbH Volker Burger has continued to dedicate himself to the further development of test methods and production processes. He contributes with his years of experience to business associations and standard committees, including the VDA 19.1 rules (Inspection of technical cleanliness) and 19.2 (Technical cleanliness in assembly).

Given the location of the company at the World Center of Medical Technology in the district of Tuttlingen and the increasing requirements and demand from the field of medical technology for tests for the surface cleanliness of medical products, it seemed an obvious choice to enter into this field.

CleanControlling Medical GmbH & Co. KG was founded in 2014 with the development and accreditation of a biological laboratory. Extensive experience from laboratory analysis in the field of technical cleanliness is an important basis for the efficient laboratory management with the highest requirements for quality and reliability, as they are demanded in the automotive sector.

CleanControlling Medical GmbH & Co. KG is a GLP-certified, DIN EN ISO/IEC 17025 accredited and ZLG-approved testing laboratory for cleanliness testing of medical products. The range of services comprises a broad range of tests with which the biological, chemical and particulate cleanliness condition of medical products is tested, culminating in validation of instructions for processing of medical devices.

OVERVIEW OF LABORATORY ANALYSIS

Suppliers, manufacturers and distributors of medical products are responsible for the quality of their products. To ensure patient safety, the hygienic, microbiological and chemical cleanliness, the biological compatibility including surface quality and increasingly the particulate cleanliness are of crucial importance.

As an accredited laboratory, CleanControlling Medical GmbH & Co. KG tests the biological, particulate and chemical surface cleanliness of medical products and validates their safe processing and sterilization.

BIOLOGICAL TESTS

- In-vitro cytotoxicity test as per DIN EN ISO 10993-5
- Determination of bioburden including validation as per DIN EN ISO 11737-1
- Endotoxin test (LAL test) as per USP 85/ Ph. Eur. 2.6.14
- Sterility test as per DIN EN ISO 11737-2
- Evaluation of contact plates for microbiological environment monitoring

PARTICULATE TESTS

Particulate contamination testing using an optical particle counter (OPC) based on USP 788 or microscopic evaluation based on ISO 16232 * or USP 788

ADDITIONAL TESTS

Analyses in collaboration with accredited partner laboratories:

- Chemical analyses, e.g. GC-MS, LC-MS, TOC, THC *
- In vitro pyrogen test (IPT) *
- Testing of the product surface, e.g. REM/EDX, XPS *
- Drinking water test as per with EN 285 *

VALIDATIONS

Tests within the validation of processing instructions for medical devices acc. to DIN EN ISO 17664

- manual or automates processing of medical devices
- steam sterilization of medical devices
- simulation of processing cycles of medical devices*

PRODUCTS

Selected products for microbiological environment monitoring and clean handling and packaging of samples

* This service does not fall within the scope of accreditation

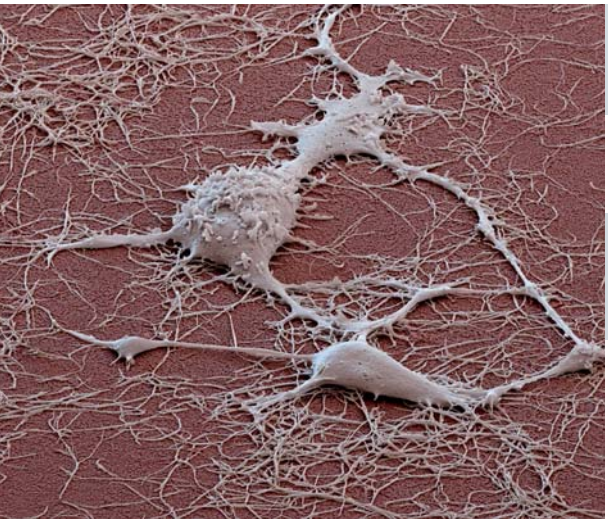
In-vitro cytotoxicity test (as per DIN EN ISO 10993-5)

The ability of a substance to damage cells or tissue is referred to as cytotoxicity.

The test for cytotoxicity is one of the most important test methods within the scope of the biological evaluation of medical devices (standard series DIN EN ISO 10993). The objective of this evaluation is the safety of the medical device with regard to its use in or on human beings. The in-vitro cytotoxicity test is of special importance here, as it detects any type of cytotoxic effect of a product, without, however, specifying the exact cause.

Fibroblasts (connective tissue cells) are used for this test, as they have a high sensitivity to toxic substances. The cells are either incubated with the product itself or with an extract of the product for several days. At the end of the incubation period, the cells are microscopically examined for morphological changes and altered growth behavior, and are then dyed to quantify the number of cells. From the ratio of the number of cells coming into contact with the product to control cells, the effect of the product on the growth (proliferation) of the cells can be determined and statements made on growth inhibition by the product.

A toxic effect can be caused by the product itself (material, coating) or by residues (e.g. of cleaning agents) or contamination on the product surface. This means that positive results in the in-vitro cytotoxicity test can lead to a number of additional tests to investigate the exact cause of the cytotoxic effect.



Fibroblasts/connective tissue cells

Test procedure

Extraction	Extraction of the product in a cell culture medium for 24 hrs
Incubation	Incubation of the resulting extract with fibroblasts (connective tissue cells) for 48-72 hrs
Measurement	Testing for growth inhibiting properties of the product with microscopic evaluation and staining of the cells
Unit	% growth inhibition

Determination of bioburden including validation (as per DIN EN ISO 11737-1)

The objective of determination of bioburden is to determine the population of viable microorganisms (bacteria and fungi) on or in a product or its packaging. The determination of this number is an important step in the validation of a sterilization process and in process-related quality tests when manufacturing and/or cleaning a medical product.

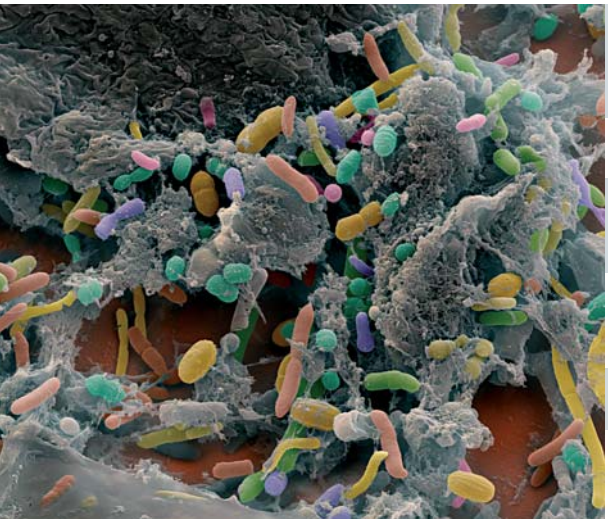
For this purpose, the product is placed in a culture medium, or it is rinsed in a sterile solution, the rinsing medium is filtered through a sterile membrane and the membrane is applied to several culture media. The culture media are incubated for several days and the microorganism colonies formed in the process are counted. The number of colonies grown is then equal to the number of colony-forming units (CFUs, individual microorganisms or groups of microorganisms adhering to each other) which were originally on the product. By using various culture media and incubation conditions, it is initially possible to roughly differentiate between bacteria and fungi. By using additional selective media, a further specification of the microorganisms found can subsequently be carried out primarily for the bacteria. This can then be used to localize the origin of contamination during the manufacturing and/or cleaning process of the product.

Validation of test method

The material and the geometry of a medical product have a major influence on the efficiency of the test method. Therefore, a one-time validation of the test method should be carried out for each product.

For this purpose, the product is inoculated with a known number of a known test organism and then tested with clearly defined parameters. At the end of the test, the CFUs found are counted and compared with the number applied. This ratio is the recovery rate. This is then used to calculate a correction factor which is calculated into all subsequently conducted bioburden determinations on this product. In accordance with the DIN EN ISO 11737-1 standard, the recovery rate should be at least 50 %, otherwise the parameters of the test method must be changed and tested again. If the recovery rate has reached a satisfactory value, all bioburden determinations on this product must be carried out with exactly the same parameters as during validation.

Test procedure



Collection of various microorganisms

Only for validation (once per product)	Inoculation of the product with a known test organism for determining the recovery rate
Extraction	Extraction of the product in a suitable medium
Filtration	Filtration of the extract through a sterile filter membrane
Incubation	Incubation of the membranes on one or more culture media for 5–7 days
Counting	Counting of the cultivated colonies
Unit	CFU (colony-forming unit)

Endotoxin test (as per USP 85 and Ph. Eur. 2.6.14)

Endotoxins (ancient Greek endo: "inside", "within", toxins, "the poisonous substance") are part of the outer cell membrane of gram-negative bacteria, which can lead to inflammation and other physiological reactions in the human body.

Endotoxins are lipopolysaccharides (LPS), i.e. compounds consisting of fat-like (lipo) components and sugar components (polysaccharides). During decomposition of the bacteria, parts of these are set free and have a toxic effect. These parts are referred to as endotoxins and, in contrast to other toxins, are not continually released by living bacteria into their environment. They are extremely heat-stable and also survive conventional sterilization processes, i.e. even sterilized products can have a high endotoxin load if they were heavily contaminated with bacteria prior to sterilization. These bacteria are killed in the process, releasing the endotoxins of the cell membrane.

The most sensitive method of endotoxin measurement is based on the use of the lysate of a certain cell type called amebocyte from the blood of the horseshoe crab (Limulus). The frequently used designation LAL test (limulus amebocyte lysate test) for testing for endotoxins also results from this. This lysate reacts on contact with endotoxins by agglutination.

Nowadays it is rather uncommon to test using the agglutination reaction. State-of-the-art technology uses the additional integration of industrial components which generate a color reaction when endotoxins are bonded which can then be measured quantitatively. The endotoxin concentration is specified in the unit EU (endotoxin units) per ml or per product.

Common limit values are 20 EU/product for products which do not come into contact with the central nervous system (CNS), 2.15 EU/product for products which come into contact with the CNS and 0.5 EU/product in eye surgery.

Molecular structure of an endotoxin

Test procedure

Extraction	Extraction of the product in endotoxin-free water
Measurement	Measurement of the endotoxin content of the extract
Analysis	Calculation of the endotoxin load per product
Unit	EU/ml - endotoxin units per milliliter, or EU per test object

Particles in medical technology (based on USP 788 or ISO 16232 *)

Particulate contamination of the products is also becoming increasingly important in medical technology. Some questions however remain without sufficient answers. Exactly what damage do particles cause in the body? What particles are especially harmful in which organs? What effect does the material have?

Among the many standards for medical technology there are various individual standards for the examination of particulate contamination on surfaces which, however, only relate to specific products or product groups in each case. In some standards the procedure for testing particulate contamination is described rather imprecisely, making a comparison of test results from different laboratories impossible. In other cases, the conditions are so rigidly specified that differing product geometries, materials and surfaces are not taken into account.

Due to the lack of standardized specifications the pharmaceutical standard USP 788 has been established as a frequently used standard for testing injection liquids in the medical product sector. USP 788 has the benefit that it specifies limit values. On the other hand, it does not describe a method for the extraction of particles from the test object as the limit values relate to liquid quantities, which then has to be translated in suitable manner for the assessment of solid objects. USP 788 favors the analysis of particles by way of a direct count in the liquid, using an optical particle counter. USP 788 also describes a microscopic method.

CleanControlling Medical GmbH & Co. KG has established the method favored in medical technology, using an optical liquid particle count based on USP 788, as an accredited analysis method. This test is particularly suitable for the validation and monitoring of cleaning processes.

Microscopic particle analyses based on DIN EN ISO 14644-9, which is established in the field of clean room technology, and in turn refers to ISO 16232 and VDA 19.1 as applied in industry, lend themselves to the examination of particles and particle sources in the manufacturing process. These particle analyses can be called upon for further tests (e.g. REM-EDX, FT-IR) for material determination of particles. For microscopic particle analyses CleanControlling Medical GmbH & Co. KG calls upon the many years of experience of CleanControlling GmbH in the field of technical cleanliness.

Particle extraction

Test procedure

Test method	Optical particle counter (based on USP 788)	Microscopic analysis (based on ISO 16232 / VDA 19.1)
Particle size	5 - 200 µm	Material microscope › 5 µm stereo microscope › 25 µm
Extraction	Removal of particles from test object using demineralized pure water	Removal of particles from test object using demineralized water
Filtration	No filtration	Filtration of the entire extraction medium to an analysis filter
Analysis	Direct count of particles in a defined quantity of extraction medium using optical particle counter (OPC)	Microscopic analysis of the analysis filter, count and measurement
Unit	Area-equivalent circular diameter of the particle in µm	Particle length (max Feret) in µm

Validation of the instructions for processing of medical devices (as per DIN EN ISO 17664)

Manufacturers and distributors of medical devices which are designed for reuse, must provide information for their products and instructions for processing of the products in order to guarantee the clean processing results required for patient safety. These also include some medical devices for single use which are sold non-sterile but are designed for use in a clean, disinfected and, if necessary, sterile condition.

As per DIN EN ISO 17664 at least one automated process must be described in these instructions, unless the medical device is not suitable for such a process. In this case a manual process must be described. These instructions must contain specifications for cleaning (with precleaning as applicable), disinfection and sterilization of the products. As per the specification in DIN EN ISO 17664 these product-related instructions have to be validated, i.e. laboratory tests must be carried out to verify that the specifications in the instructions genuinely result in the product having a cleanliness condition with which it can be safely re-used on patients.

The validation of the instructions is performed by applying a defined test contamination to the product (e.g. a mixture of blood and bacteria), with areas of the product which are difficult to access being afforded particular attention, and subsequently cleaning and disinfecting the product exactly in accordance with the specifications in the product-related instructions. The specifications of the instructions must be so exact that as far as possible the party performing the test cannot influence the results.

The success of the cleaning step is tested by measuring the reduction of protein and bacteria contamination on the product. The success of disinfection can be determined from the reduction of a test organism suitable for testing disinfection.

Instruments in washer-disinfector

Test procedure

Contamination	Inoculation of the product with a test contamination (e.g. mixture of blood and bacteria)
Precleaning	If applicable, manual precleaning of the product before automated processing
Processing	Manual or automated (washer-disinfector) cleaning and disinfection
Assessment of cleaning	Visually clean; residual protein ‹ 100 g, reduction of the bioburden by at least 2-4 log steps
Assessment of disinfection	Determination of residual bioburden

Validation of the instructions for sterilization of medical devices (as per DIN EN ISO 17664)

In the same way as with processing of medical devices (cleaning and disinfection) the manufacturer or the distributor must describe and provide a suitable sterilization method if the medical device is designated for sterilization.

To achieve the required sterility safety level the medical device manufacturer must indicate at least one validated sterilization method which meets the requirements of an international standard wherever possible, e.g. damp heat (ISO 17665).

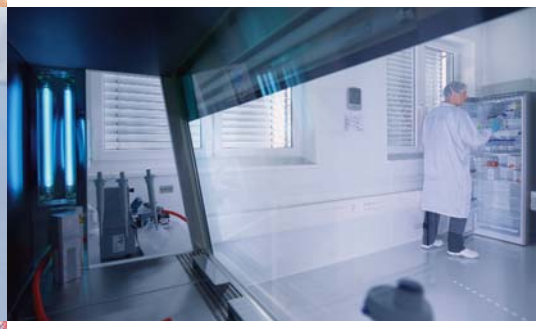
To verify the suitability of the sterilization method indicated in the product-related instructions the sterile product is inoculated with the spores of very heat-resistant bacteria Geobacillus. The inoculated product is packaged in accordance with the specifications (primary and, if applicable, secondary packaging) and then sterilized with steam with the specified parameters.

The steam sterilization is performed in a half-cycle process (e.g. 134°C, 2.5 minutes). The success of sterilization is then tested by inserting the product in a liquid culture medium for 7 days. The culture medium must not show any signs of bacteria growth, i.e. it must not be clouded.

Biology laboratory

Test procedure

Contamination	Inoculation of the product with spores of Geobacillus stearothermophilus, areas of the product which are difficult to access by the steam must be afforded particular attention
Sterilization	Steam sterilization of the product as per specifications of the manufacturer (in half-cycle process)
Assessment of sterilization	Examination of the sterility using incubation of the product in a liquid culture medium for 7 days → there must be no visible growth of microorganisms



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