Be on the safe side: Evaluation of cleaning procedures for medical devices employing TOC measurement

Markus Janssen, Shimadzu Europa GmbH, Duisburg, Germany.
Correspondence email: mja@shimadzu.eu

The European Parliament has adopted a new Medical Device Regulation MDR 2017/745 [1]. Sophisticated quality management systems now become an obligation and help to increase patient safety by reducing the risk of unsafe medical devices. Recently, the press has reported on problems that have occurred [2]. The international standard ISO 19227 'Implants for surgery - Cleanliness of orthopaedic implants' [3] is a guidance document intended to assist manufacturers addressing this topic by employing risk management and suitable analytical test methods.

Advances in pharmaceutical technology, such as the new mRNA vaccines, are currently the talk of the town. For many people, they are the hope of a way out of the pandemic, for others a reason for skepticism and concern - certainly influenced by the fact that they are based on new concepts that are difficult to grasp in the truest sense of the word. However, modern medicine uses not only drugs to treat patients, but also various pieces of 'hardware', the so-called 'medical devices'.

Medical devices are items intended for the diagnosis, prevention or treatment of illnesses and injuries by non-pharmacological means. This includes a wide variety of products from household thermometers to surgical instruments, pacemakers and artificial hip joints, just to name a few. They are critical tools that support or even enable the recuperation of patients from a variety of afflictions, ranging from broken bones and joint injury to heart diseases and spinal trauma.

And their importance continues to grow: According to the 'Organisation for Economic Co-operation and Development' (OECD), for example, the number of knee replacements has doubled in their member states since 2000 [4]. The need for suitable products is high, however the requirements imposed on medical devices are strict, and with good reason.

The EU Medical Device Regulation MDR 2017/745

The European Commission has passed a new medical device regulation MDR 2017/745, which is therefore to be applied as a trans-national law in all EU countries. It regulates the marketing and commissioning of medical devices and accessories for human use and replaces the previous Medical Device Directive (MDD) 93/42/EEC and Directive on Active Implantable Medical Devices (AIMD) 90/385/EEC. Manufacturers are directly responsible for compliance with the new regulation and will be subject to larger changes, including stricter clinical post-marketing surveillance.

Unannounced audits and product inspections are intended to help reduce the risk of unsafe medical devices and to increase patient safety. Sophisticated quality management systems thus become an obligation. After transitional periods and a one-year postponement due to the COVID-19 pandemic, the new MDR became effective on 26th May 2021.

Risk reduction is key

Of all medical devices, joint replacements probably have the longest period of use. At best, such an implant can remain in the human body for many years, as a 10-15 year lifetime is usually achieved, while cases of implants over 25 years old are not uncommon.

To achieve this, the materials used in prosthetics must meet a variety of requirements such as durability, sterilisability and, above all, compatibility with the human body. Only well-suited materials and products that have little or no negative effect on the organism are referred to as 'biocompatible'. To determine biocompatibility, substances and implants are tested in laboratory trials to determine their compatibility with the human body.

These elaborate test series are part of the strict approvals for implants worldwide. The introduction of foreign substances and objects into the human body always represents a risk for patients, which must be reduced as far as possible - post-operative infections or long-term damage caused by heavy metal poisoning would be catastrophic. Even after the product has been found suitable for approval, the utmost care in the form of cleanliness and hygiene is of great importance. This starts during the production phase at the manufacturer.

Cleanliness in the production of orthopedic implants

Cleaning is generally essential to remove contamination after manufacturing processes. The cleaning methods, however, must not interact with materials and impair their biocompatibility, or compromise the effectiveness of the implant. In addition, cleaning agents should effectively be removed unless it is proven that they do not have a negative impact.

Helpful in this regard is the Norm ISO 19227 'Cleanliness of Orthopedic Implants - General Requirements', published in March 2018. It may be regarded as a guideline to assist manufacturers of specifically orthopaedic implants in addressing this issue.

It covers general requirements from risk assessment and validation of cleaning methods to sampling, and prescribes a series of tests to demonstrate cleanliness throughout the entire production process. These include test methods to identify inorganic and particulate contaminants, organic contaminants, bioburden and systematic visual checks.

Total contamination in a single analytical value

To determine organic contamination, the sum parameter TOC (Total Organic Carbon) has been established for decades. It indicates the total concentration of organic compounds in a single analytical value. TOC measurement does not identify contaminants but does reflect the total organic contamination caused by by-products of the manufacturing process such as grease or lubricants, detergents and disinfectants as well as natural organic matter (biological contaminants). A prerequisite is good water solubility of the substances to be tested. The parameter is common practice in cleaning validation for pharmaceutical production plants [5].

In the most commonly used method for the determination of TOC, the water sample is first acidified with a mineral acid. In this process, inorganic carbon compounds such as carbonates or hydrogen carbonates are converted to carbon dioxide which is then removed by a sparge gas.

An aliquot of the prepared sample is injected onto a hot catalyst. This oxidises organic carbon compounds to CO_2. A carrier gas takes the CO_2 to an NDIR detector, which quantifies the amount of carbon dioxide.

The process is quick and easy with an analysis time of about 4 minutes per injection. Modern TOC analysers, such as the TOC-L from Shimadzu *(Figure 1)*, carry out fully automated sample preparation. Oxidation of the organic components is performed employing a highly effective platinum catalyst at a temperature of 680°C. An automatic dilution function enables the creation of multi-point calibrations from a stock solution.

Figure 1. TOC-L from Shimadzu.

Monitoring of water-soluble organic impurities by TOC

To assess the cleanliness of orthopaedic implants, samples were extracted in a suitable solvent and then analysed. For organic impurities with TOC, the extraction is carried out with water. The extraction conditions, mainly temperature and time, should be selected with the aim to represent the compounds extracted over the duration of medical devices use. They shall to be justified and documented.

However, the ISO standard does not contain extraction procedures, but refers to relevant standards such as ISO 10993-12 [6] in which extraction conditions are described. If no historical data on TOC results is available to the manufacturer of the implants, a limit value of 0.500 mg TOC / implant as mentioned in the standard serves as a starting point for acceptance levels. The final limit shall be determined after a dedicated risk assessment taking into account factors such as the size of the implant, detergents used and potential sources of hazard.

In a practical example, the femoral component of a knee implant *(Figure 2)* was extracted in a beaker for one hour with 250 mL ultrapure water (70°C) in an ultrasonic bath. A second beaker of water (without implant) was used to determine a blank value. Subsequently, the TOC concentration of both water samples was examined. Results are shown in the Table 1. The tested implant complies with the limit value of 0.500 mg per implant as specified in ISO 19227.

Figure 2. Artificial knee joint.

In further tests, two implants were deliberately contaminated. In one case, an implant was placed in a glucose solution (50 mg/L) and then dried. A different implant was contaminated by briefly 'just touching' it (without gloves for about 2 seconds). Both implants were subsequently extracted and analysed as described above (one hour / ultrasonic bath / 70°C / 250 mL water). As expected, the limit value of 0.500 mg per implant was clearly exceeded in test 2 (contamination by glucose solution).

In test 3, the result complies with the limit, but an increase in contamination due to brief contact with the implant without suitable protective gloves can be clearly observed. The results of the tests are summarised in *Table 1*.

Table 1. Result of TOC Analysis of femoral implant components.

Sample	TOC [mgC/L]	TOC minus "BV" [mgC/L]	TOC per implant [µgC]
Ultrasonic bath blank value "BV"	0.64	—	—
Clean implant	1.98	1.34	0.335
Soiled using glucole	3.46	2.82	0.705
Soiled by brief touch	2.48	1.84	0.46

To quantify substances that are not water-soluble according to ISO 9377-2, analysis with GC-FID after extraction in non-polar solvents is a suitable method. Alternatively, entire components such as smaller plates and screws for surgery as a whole could be examined for organic contamination in the TOC solid sampling module.

Direct evaluation of organic contamination

While not in the scope of ISO 19227, it is possible to analyse organic contamination of medical devices without the need for liquid extraction. Provided the sample to be measured is small enough, it can be introduced into a solid sample measurement system. This can be suitable for smaller metallic parts such as spinal fixations, bone screws or small surgical instruments *(Figure 3)*.

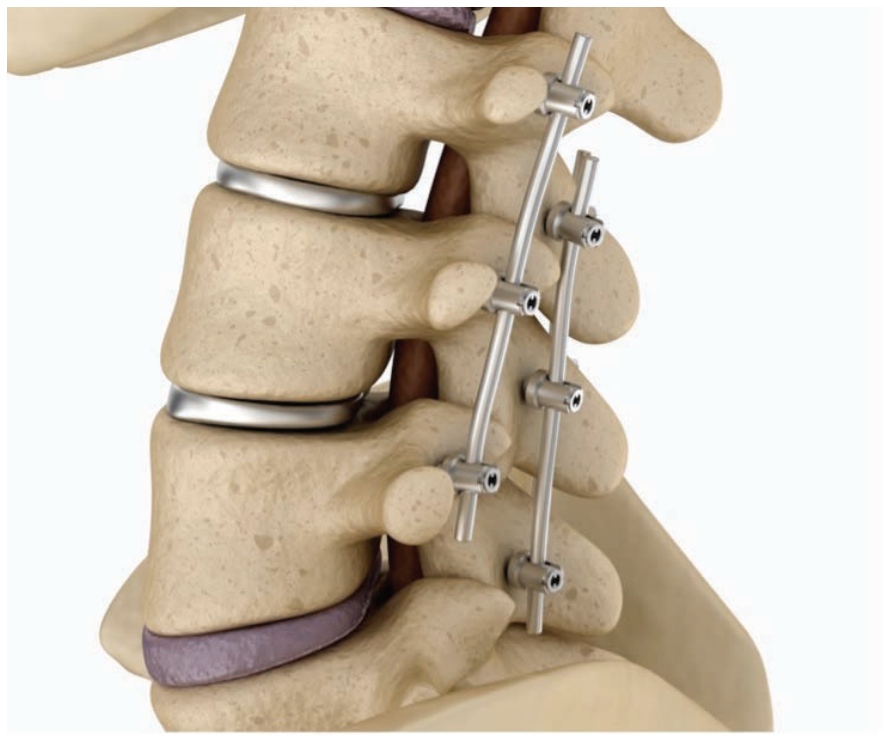

Figure 3. Spinal fixation parts.

For the direct combustion of solid samples, Shimadzu's TOC-L analyser is combined with the SSM-5000A solids sampling module. Samples are introduced into a 900 °C hot furnace where carbon is oxidised to CO_2 under the presence of catalyst and oxygen atmosphere. The analysis can be considered as destructive.

In an experiment, two small medical devices were prepared after cleaning as samples. Both medical device A and B were cut to lengths of approximately 3 cm and placed in ceramic sample boats. They were subsequently analysed for total carbon in the solid sampling system. The results in *Table 2* show excellent sensitivity.

Table 2. Results of direct combustion.

Sample name	Total carbon [µgC]
Medical device A	8.239
Medical device B	40.42

Summary

TOC analysers are reliable companions for sophisticated quality control in the production of medical devices and help to increase patient safety. For various other test methods listed in ISO 19227, such as ICP-MS/OES for inorganic contaminants and GC-FID or FTIR for water-insoluble organics, Shimadzu offers high-performance solutions as well.

References

1. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, Document 32017R0745 https://eur-lex.europa.eu/eli/reg/2017/745/oj

2. International Consortium of Investigative Journalists (ICIJ) - Implant files https://www.icij.org/investigations/implant-files/

3. ISO 19227:2018 Implants for surgery - Cleanliness of orthopedic implants - General requirements

4. OECD "Health at a Glance 2019 report". Page 41, Figure 2.1, OECD Library ISBN 9789264807662 https://www.oecd.org/els/health-systems/health-at-a-glance-19991312.htm

5. United States Food and Drug Administration (FDA) – Questions and Answers on Current Good Manufacturing Practices – Equipment https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practices-equipment#TOC

6. ISO 10993-12:2021 Biological evaluation of medical devices - Part 12: Sample preparation and reference materials