CEN

WORKSHOP

AGREEMENT

CWA 17253-2

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English version

Joint implants - Part 2: Tiered toolkit approach to evaluate the biological impact of wear particles from joint replacements and related devices

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Contents

Page

European foreword

CWA 17253-2 was developed in accordance with CEN-CENELEC Guide 29 "CEN/CENELEC Workshop Agreements – The way to rapid agreement" and with the relevant provisions of CEN/CENELEC internal Regulations – Part 2. It was agreed in a Workshop on 2017-09-26 to 2017-09-28 by representatives of interested parties, approved and supported by CEN following a public call for participation made on 2017-06-15. It does not necessarily reflect the views of all stakeholders that might have an interest in its subject matter.

The final text of CWA 17253-2 was submitted to CEN for publication on 2018-01-30. It was developed and approved by the following organizations listed below:

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Those CEN Technical committees supporting technical consensus are as follows:

- CEN/TC 206, *Biological and clinical evaluation of medical devices*
- CEN/TC 285, *Non-active surgical implants*

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The secretariat was held by the British National Standards Institution (BSI).

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Comments or suggestions from the users of the CEN Workshop Agreement are welcome and should be addressed to the CEN-CENELEC Management Centre.

Introduction

Articulating human joint replacements for hips and knees currently constitute a global market exceeding 15 billion USD p.a., which is expected to rise as demographics reflect an ageing population [1]. Furthermore, a significant number of revision operations are performed, with 97 569 hips and 60 818 knees revised between April 2003 and December 2016 in the UK (excluding Scotland) [2]. The most commonly recorded indication for revision is aseptic loosening [2], which has been shown to be often associated with the presence of wear particles [3]. In addition, adverse or extreme loading has been shown to have a detrimental effect on implant function [4,5]. Thus, device failure still occurs too frequently, leading to the conclusion that it is necessary for both longevity and reliability of implants to be improved. Improvements in implant performance have resulted from enhanced clinical practice (many failures are directly attributable to imprecise or inadequate surgical procedures) [6], improvements in resistance to wear and corrosion, and the ability of the articulating surfaces to resist mechanical damage.

Whilst improved wear resistance might enhance device longevity [7], in the future such devices are likely only to be successfully placed on the market if, amongst other requirements, the size, volume, morphology and biological impact of wear debris generated during the anticipated functional life of the implant are assessed [8]. Wear is usually assessed on the basis of short- to medium-term joint simulator studies, performed according to international standards, e.g. ISO 14242-1:2014, ISO 14243-3:2014, ISO 18192-1:2011 and ISO 18192-3:2017, from which the wear particles generated per million cycles are isolated, again following international standards such as ISO 17853:2011. However, it is also crucial to determine the biological impact of released particles in order to predict the long-term clinical performance of an implanted device, since the release of wear particles and cellular responses to these released particles have been widely associated with total joint replacement failure [9-12].

Evaluation of the biological response to wear particles is typically undertaken using cytotoxicity assays, such as those that require conversion of a substrate by live cells to affect a colour change, e.g. the tetrazolium salt used for assessing cell metabolic activity (MTT) assay[1)] or produce light that can be quantified, e.g. the adenosine triphosphate (ATP) assay [13]. However, cytotoxicity is a tool which only assesses cells as either alive or dead. Therefore some cells might undergo damage such as deoxyribonucleic acid (DNA) damage or oxidative stress (production of reactive oxygen species), which while not immediately cytotoxic, could accumulate over time causing adverse future events such as tumour formation. The regulatory landscape is changing: in order to achieve Food and Drug Administration (FDA) approval, joint implant manufacturers are now required to test cellular responses to wear particles, if the release of such wear particles is likely to be linked to implant failure [8], where previously only biological evaluation of the bulk material was required. However, there are currently no standards pertaining to the testing of particles in biological systems. In addition, not all assays are suitable for use with all wear particles. For example, certain optically dense materials, e.g. metals such as cobalt-chromium-molybdenum alloy have been observed to interfere with output readings that rely on optical density, whilst others, e.g. alumina ceramics, have been shown to convert substrates to chromogenic products in the absence of cells. Therefore, there is a need to develop an approach to measure the biological impact of wear particles that goes beyond cytotoxicity (covered by ISO 10993-5:2009) to capture a broader range of cellular effects. It is timely to agree an approach that could satisfy the regulators to allow more informative pre-clinical assessments of the biological effects of wear particles from different materials.

1) An ISO standard is currently in development: ISO 19007, *Nanotechnologies – In vitro MTS assay for measuring the cytotoxic effect of nanoparticles.*

1 Scope

This CEN Workshop Agreement (CWA) provides a tiered approach for evaluating the biological impact *in vitro*, of wear particles generated in joint replacements and related medical devices, such as screws and trauma plates used in treating fractures. The approach is based on existing, well established test methods that have been widely employed to assess wear particle responses, including: a cell viability assay to assess cytotoxicity; enzyme linked immunosorbent assay (ELISA) to assess inflammatory cytokine release; an oxidative stress assay to assess release of reactive oxygen species (ROS); and a comet assay to assess damage to DNA.

This CWA does not cover the following:

a) the biological evaluation of the bulk materials from which medical devices are manufactured;

b) procedures for the isolation of wear particles from joint replacements and related medical devices, which are the subject of CWA 17253-1; and

c) safety issues associated with the execution of the assays covered by CWA 17253-2 or the health and well-being of recipients of joint replacements.

This CWA is for use by manufacturers of joint replacements evaluating new and existing materials and designs for human joint replacements and related devices, commercial, industrial and academic laboratories undertaking evaluation of, and studies into, device and material performance, and might be of use to other organizations, including regulators, concerned with the potential impact on the health and well-being of recipients of joint replacements.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ASTM F1537-11:2011, *Standard Specification for Wrought Cobalt-28Chromium-6Molybdenum Alloys for Surgical Implants (UNS R31537, UNS R31538, and UNS R31539)*

CWA 17253-1:2018, *Joint implants — Part 1: Novel methods for isolating wear particles from joint replacements and related devices*

EN 12469, *Biotechnology — Performance criteria for microbiological safety cabinets*

EN ISO 8655-2:2002/AC2009, *Piston-operated volumetric apparatus — Part 2: Piston pipettes (ISO 8655-2:2002/Cor 1:2008)*

ISO 29701:2010, *Nanotechnologies — Endotoxin test on nanomaterial samples for in vitro systems — Limulus amebocyte lysate (LAL) test*

3 Terms, definitions and abbreviations

3.1 Terms and definitions

For the purposes of this document, the terms and definitions given in CWA 17253-1:2018 and the following apply.

3.1.1
agglomerate
group of particles held together by relatively weak forces, including van der Waals forces

[SOURCE: ISO 18158:2016, 2.1.4.9, modified]

3.1.2
aggregate
heterogeneous particle in which the various components are held together by relatively strong forces and thus not easily broken apart

[SOURCE: ISO 18158:2016, 2.1.4.10]

3.1.3
clinically relevant dose
volume of particles per cell which has been observed in a clinical situation

3.1.4
complete culture medium
culture medium containing 10 % foetal bovine serum, 2 mM L-glutamine, 100 µg.ml-1 streptomycin and 100 U.ml-1 penicillin

3.1.5
device
joint replacement and any related medical devices

Note 1 to entry: Related medical devices are implanted devices, which have the potential to produce wear particles, for example screws and trauma plates used in treating fractures.

3.1.6
model particles
particles with comparable physico-chemical characteristics to those generated clinically

Note 1 to entry: Comparable physico-chemical characteristics include the size range, size distribution, shape and chemistry of wear particles.

3.1.7
replicate
analyses performed simulataneously with different portions of the same sample to obtain an independent measurement

3.1.8
verified wear particle generation process
wear process demonstrated to produce particles with comparable physico-chemical characteristics to those generated clinically

Note 1 to entry: Comparable physico-chemical characteristics include the size range, size distribution, shape and chemistry of wear particles.

3.2 Abbreviations

For the purposes of this document, the following abbreviations apply.

ATP adenosine triphosphate

CO	cell-only
CoCrMo	cobalt-chromium-molybdenum alloy
DCFDA	2',7'-dichlorofluorescein diacetate
DMEM	Dulbecco's Modified Eagle's medium
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme linked immunosorbent assay
FBS	foetal bovine serum
FDA	Food and Drug Administration (US)
GM-CSF	granulocyte-macrophage colony stimulating factor
HBSS	Hank's Balanced Salt Solution
IL-1β	interleukin-1β
IL-6	interleukin-6
IL-8	interleukin-8
IL-10	interleukin-10
IL-12p40	interleukin-12p40
LPS	lipopolysaccharide
MCP-1	Monocyte chemotactic protein 1
MTT	tetrazolium salt used for assessing cell metabolic activity
PBMNC	peripheral blood mononuclear cell
PBS	phosphate buffered saline
PO	particle-only
ROS	reactive oxygen species
RPMI 1640	Roswell Park Memorial Institute 1640 medium
SEM	scanning electron microscopy
Ti6Al4V	titanium-aluminium-vanadium alloy containing 6 % aluminium and 4 % vanadium
TJR	total joint replacement
TNF-α	tumour necrosis factor alpha
UHMWPE	ultrahigh molecular weight polyethylene
% v/v	volume concentration expressed as percent volume to volume

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