



Designation: F1904 – 23

Standard Guide for Testing the Biological Responses to Medical Device Particulate Debris and Degradation Products *in vivo*¹

This standard is issued under the fixed designation F1904; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ϵ) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 The purpose of this standard guide is to describe the principles and approaches to testing of medical device debris and degradation products from device materials (for example, particles from wear) for their potential to activate a cascade of biological responses at local and systemic levels in the body. In order to ascertain the role of device debris and degradation products in stimulating such responses, the nature of the responses and the consequences of the responses should be evaluated. This is an emerging area. The continuously updated information gained from the testing results and related published literature is necessary to improve the study designs, as well as predictive value and interpretation of the test results regarding debris/degradation product related responses. Some of the procedures listed here may, on further testing, not prove to be predictive of clinical responses to device-related debris and degradation products. However, only the continuing use of standard protocols will establish the most useful testing approaches with reliable study endpoints and measurement techniques. Since there are many possible and established ways of determining the debris/degradation product related responses *in vivo*, a single standard protocol is not stated. However, this recommended guide indicates which testing approaches are most applicable per expected biological responses and which necessary information should be supplied with the test results. To address the general role of chronic inflammation in exaggerating device-related foreign body response (FBR), the recommendations in this standard include the assessment of device-related pro-inflammatory responses and subsequent tissue remodeling potential.

1.2 This document is to provide the users with updated scientific knowledge that may help better characterize medical device debris related responses. It is to help the users to optimize their plans for particle characterization and biocom-

patibility assessment by considering the testing principles and methods available in published literature that are appropriate to their products.

1.3 This standard is not sufficient to address device-related degradation products that result in gas formation or that are exclusively represented by nanoparticles, or soluble species such as dissolved metal ions.

1.4 While devices should be designed and manufactured in such a way as to reduce as far as possible the risks posed by substances or particles (including wear debris, degradation products, and processing residues) that may be released from the device, this standard guide may help users to identify the presence of wear debris and degradation products and subsequent adverse reactions that may occur.

1.5 Although this guide is based on the available device debris-related knowledge that is largely based on orthopedic devices, most of the recommendations are also applicable to other (non-orthopedic) device areas.

1.6 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.7 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 ASTM Standards:²

F561 Practice for Retrieval and Analysis of Medical Devices, and Associated Tissues and Fluids

F619 Practice for Extraction of Materials Used in Medical Devices

¹ This guide is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.16 on Biocompatibility Test Methods.

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² For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

F748 Practice for Selecting Generic Biological Test Methods for Materials and Devices

F1877 Practice for Characterization of Particles

F1903 Practice for Testing for Cellular Responses to Particles *in vitro*

2.2 *ISO Standards*:³

ISO 14242-1 Implants for surgery—Wear of total hip-joint prostheses—Part 1: Loading and displacement parameters for wear-testing machines and corresponding environmental conditions for test—Amendment 1

ISO 14242-3 Implants for surgery—Wear of total hip-joint prostheses—Part 3: Loading and displacement parameters for orbital bearing type wear testing machines and corresponding environmental conditions for test

ISO 14243-1 Implants for surgery—Wear of total knee-joint prostheses—Part 1: Loading and displacement parameters for wear-testing machines with load control and corresponding environmental conditions for test

ISO 14243-3 Implants for surgery—Wear of total knee-joint prostheses—Part 3: Loading and displacement parameters for wear-testing machines with displacement control and corresponding environmental conditions for test

ISO 17853 Wear of implant materials—Polymer and metal wear particles—Isolation and characterization

ISO 22622 Implants for surgery—Wear of total ankle-joint prostheses—Loading and displacement parameters for wear-testing machines with load or displacement control and corresponding environmental conditions for test

3. Terminology

3.1 *Definitions of Terms Specific to This Standard*:

3.1.1 *mechanistic, adj*—of or relating to the theory of mechanism which, in the science of biology, is defined as a system of causally interacting parts and processes that produce one or more effects.

3.1.2 *phagocytosable, adj*—capable of being phagocytosed.

4. Summary of Guide

4.1 Evaluation of biological responses to medical device debris and degradation products may be performed using specimens from animals being tested in accordance with Practice **F748** which provides recommendations for biocompatibility assessment including local and systemic toxicity. When biocompatibility testing is performed (for example, implantation or injection of the test material), evaluation of the tissues surrounding the application site represent the best opportunity for assessing FBR and other local tissue responses. Bodily fluids such as blood and urine, as well as different organ tissues from the tested animals should be used for the assessment of systemic responses. Procedures according to Practice **F561** may be used to assess the cellular and tissue responses *in vivo*.

4.2 Biological responses to device-related wear debris and degradation products may be tested using materials or extracts in accordance with Practice **F619**. The increased surface area

of small particles may enhance the amount of extracted substances but, since the response to particles may be related to the physical size, shape, composition, and dose, the use of only extracts will not completely address the question of the impact of particle formation on the tissue response, and actual implantation or other testing of particles should be included as a part of the characterization of tissue response when particle generation is likely during actual usage. These materials or extracts may be used for the *in vivo* tests described here or *ex vivo* / *in vitro* approaches described in Practice **F1903**. Particles and other device-related debris/degradation products generated by alternative methods (for example, from animal studies, clinical use, or *in vitro* studies) may also be used, if appropriately justified. The method of generation must be described.

5. Significance and Use

5.1 This standard guide is to be used to help assess the biocompatibility of materials used in medical devices (for example, externally communicating, implants, and other body contact medical devices). It is designed to test the effect of particles and other wear debris and/or degradation products on the generation of FBR and other (local and systemic) host responses of immune/inflammatory origin.

5.2 The appropriateness of the selected testing methods should be carefully considered by the user since not all materials or applications need to be tested by this guide. Existing biocompatibility screening methods may not be fully predictive of the human response, and testing approaches such as those described here are needed for continuous improvement of the predictability of biocompatibility testing. The effectiveness of animal testing in terms of its predictability of human outcomes is dependent on the study design. If possible, study endpoints should be chosen to minimize interspecies variability and to investigate clinically relevant biological responses. While testing approaches should remain at the user's discretion, the following should be taken into consideration when selecting most appropriate tests and study endpoints.

5.2.1 Device-induced responses usually involve both innate and adaptive immunities, which raises possible need for specific testing for each of these immune response types.

5.2.1.1 Device-related adaptive immune responses are mostly due to lymphocyte-mediated delayed-type hypersensitivity. *In vivo* allergenicity to a test material (which can be introduced via different routes) should be assessed by monitoring for any signs of allergic and acute toxicity reactions, for example, scratch, tremor, and dyspnea. In addition, *ex vivo* analysis on immunophenotyping of the isolated splenocytes/lymphocytes from the same studies should be considered.

5.2.1.2 Device-related innate immune responses are mostly mediated by macrophages and can be assessed by histopathological assessment of the extent of FBR including macrophage accumulation around the test material. Supplementary *ex vivo* / *in vitro* assessment can be used for additional macrophage-based testing such as macrophage immunophenotyping (proinflammatory M1 and anti-inflammatory/wound healing M2) as well as debris uptake by phagocytes (phagocytosability) involving the entire range of test material characteristics.

³ Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, <http://www.ansi.org>.