Designation: F3306 – 19

Standard Test Method for Ion Release Evaluation of Medical Implants[1]

This standard is issued under the fixed designation F3306; 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 This test method assesses metal or other ions released from single-use, metallic, implantable medical devices, or components thereof, by exposing the device to solutions simulating the in-vivo environment and temperature in a container for a predetermined time frame with regular sampling at adequate intervals. Examples of device types that may be evaluated by this test method include, but are not limited to: cardiovascular devices, endovascular devices, and orthopedic implants. Devices which are to be partially implanted, but in long-term contact within the body (such as external fixation devices) may also be evaluated using this method.

1.2 This test method is used to assess devices or device components, or both, in their final form and finish, as they would be implanted. For modular implants, consideration should be given to individual testing of every part.

1.3 This test method covers the selection of specimens, specimen preparation, test environment, method of exposure, and method for evaluating the results to characterize ion release. Because of the variety of configurations and sizes of implants, a variety of specimen container configurations may be used.

1.4 This test method is not intended for ions only adsorbed onto the surface of the samples.

1.5 This test method does not apply to absorbable metallic implants (for example, magnesium-based stents, bone screws, etc.) that are intentionally designed to degrade in-vivo.

1.6 This test method does not cover the required subsequent chemical analysis, for example, by inductively coupled plasma mass spectrometry (ICP-MS), or the validation of the analytical instrumentation.

1.7 This test method does not cover the influence of dynamic loading and associated surface damage or wear on ion release. Ion release may change under dynamic loading conditions and wear. Additional testing may be required, depending on the application and outcome of this test method.

1.8 *Units*—The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

1.9 *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.*

1.10 *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]

D1193 Specification for Reagent Water

F2129 Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices

F3044 Test Method for Evaluating the Potential for Galvanic Corrosion for Medical Implants

2.2 *ISO Standards:*[3]

ISO 3696 Water for analytical laboratory use – Specification and test methods

ISO 10993-15 Biological evaluation of medical devices – Part 15: Identification and quantification of degradation products from metals and alloys

ISO 10993-17 Biological evaluation of medical devices – Part 17: Establishment of allowable limits for leachable substances

3. Terminology

3.1 *Definitions:*

3.1.1 *blank, n*—a sample of the test solution prepared without the specimen for baseline determination in the subsequent analysis.

[1] This test method is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.15 on Material 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.

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

3.1.2 *method detection limit (MDL), n*—the minimum concentration of an analyte that can be identified, measured, and reported with 99 % confidence that the analyte concentration is greater than zero. This confidence level is determined from analysis of a sample in a given matrix containing the analyte(s) (**1**).[4]

4. Summary of Test Method

4.1 To quantify ion release from the device over time, successive immersion testing is conducted on the same device. Initially, the device is placed in an appropriate container, filled with an appropriate simulated physiological solution, and stored at a physiological temperature for a predetermined time frame. At subsequent predetermined intervals, the immersion procedure is repeated by removing the test sample from the container, sampling the media for chemical analysis, and placing the test sample into a container with fresh media.

5. Significance and Use

5.1 Components of implanted medical devices can release ions, which may lead to adverse biological effects if released in sufficient quantities. Therefore, it may be necessary to characterize the ion release behavior over time to verify that a medical device or device components, or both, will not pose an unacceptable risk to patients. Some examples of when time-dependent ion release testing should be considered include:

5.1.1 New materials,

5.1.2 New applications (for example, different in-vivo environments or new designs) that may degrade corrosion resistance,

5.1.3 Manufacturing processes that may lead to increased ion release susceptibility,

5.1.4 Results of other corrosion testing (for example, Test Methods F2129 and F3044) indicate high susceptibility to corrosion.

5.2 Forming and finishing steps used to create an implantable device may have significant effects on the ion release behavior of the material from which the device is fabricated. Preconditioning can impact the ion release behavior of implants; therefore, prior to testing, devices should be subjected to preconditioning that is appropriate to their application. A justification shall be provided if preconditioning is omitted. Additional information on preconditioning is found in Appendix X1. Substitute test articles (tubes, plates, wires, device subcomponents, etc.) may be used for testing with adequate justification, if all processing steps, including sterilization and preconditioning, are comparable to the finished device.

5.3 To accommodate the wide variety of device shapes and sizes likely to be encountered, various sizes and shapes of containers manufactured from various materials can be used. The container material choice should be justified.

5.4 Note that the test conditions described in this test method may not completely simulate those encountered in vivo (cells, proteins, mechanical loading, and other specifics of the in-vivo environment); however, the results of this testing conducted in simulated physiological solutions can provide useful data to estimate exposure as part of a risk assessment (for example, as per ISO 10993-17) or to compare different device materials, designs, or manufacturing processes.

6. Apparatus

6.1 Water bath, oven, or heating chamber/cabinet, calibrated in the relevant temperature range to maintain the test solution temperature at 37 °C ± 2 °C.

6.2 Clean, non-metallic apparatus (for example, tweezers, string, or similar means) that can be used to transfer a sample from one container to the next.

6.3 Plastic ware or glassware for making solution.

NOTE 1—In general, whatever apparatus that will come into contact with the samples (that is, glassware, tweezers, etc.) must be appropriately clean (see 10.1.1).

7. Specimen Containers and Pouches

7.1 There are a variety of containers, pouches, and caps that may be used in this test method. The size and design of the containers and caps should be chosen accordingly and justified.

NOTE 2—Containers and pouches will both be generalized as containers for this test method.

7.1.1 To allow complete immersion of the sample being tested.

7.1.2 To contain enough fluid volume to allow analysis.

7.1.3 To contain sufficient volume to accommodate dissolution limits of the analyzed ions.

7.2 The determined volume should be used consistently throughout the test.

7.3 The container material should be selected such that the likelihood of ions adhering to or diffusing into the container wall can be neglected. Therefore, the container walls should be smooth and manufactured of a suitable material. This can be evaluated by performing a spike and recovery test as described in Appendix X2. Such validation testing should be performed and included in the test report. A justification shall be provided if validation testing is not conducted.

7.4 Pre-cleaned containers may be used in the as-received conditions. Pre-cleaned vials shall meet or exceed requirements of a Level 3 container per the U.S. EPA "Specifications and Guidance for Contaminant-Free Sample Containers" (that is, pre-cleaned with a certificate of analysis) (**2**). Certified metal-free containers are acceptable for use without pre-cleaning for analysis of metal ion release. For cleaning non-pre-cleaned containers, please refer to Section 10.

7.5 Borosilicate glass, soda lime glass, or other non-metallic containers (Polypropylene (PP), Perfluoroalkoxy alkane (PFA), etc.) can be used.

NOTE 3—Container materials can release ions themselves. Containers should be chosen according to the intended ions to be measured. For an example of how containers can be tested for suitability, see Appendix X2.

NOTE 4—Some media might need sterilized containers to prevent growth of microorganisms.

7.6 The container should be adequately closed and sealed to prevent leakage or evaporation, or both, of the test solution.

[4] The boldface numbers in parentheses refer to the list of references at the end of this standard.

8. Reagents

8.1 Reagent-grade chemicals shall be used for this test method when they are commercially available (for example, some components in bile solutions are not available in reagent-grade). Such reagents shall conform to the specifications of the Committee on Analytical Reagents of the American Chemical Society.[5] A justification shall be provided if reagent-grade chemicals are not used.

8.2 Water shall be distilled or deionized conforming to the purity requirements of Specification D1193, Type IV reagent water, or better.

NOTE 5—ISO 10993-15 requires Grade 2 water (ISO 3696) or better as the basis for its test media. If tests need to comply with the immersion test described in ISO 10993-15, the water needs to be at least Type III according to Specification D1193, if the total silica content of the used water is below 20 µg/L.

8.3 If possible, buffered solutions should be used to avoid excursions in pH. An example of a phosphate-buffered saline (PBS) formulation is given in Appendix X2 of Test Method F2129. Other simulated physiological solutions are permitted, depending on the ultimate use of the device in the body. For reference, other test solution formulations are also provided in Appendix X2 of Test Method F2129.

NOTE 6—Some media might need sterilization and a specialized work environment to prevent growth of microorganisms.

NOTE 7—These test fluids were chosen not because they are the most realistic, but because they are the most likely to reflect the worst possible outcome and because they make quantitative analysis simpler.

9. Test Specimens

9.1 Unless otherwise justified, all samples selected for testing should be taken from as-manufactured, clinical-quality product. Cosmetic rejects or other nonclinical samples may be used if the cause for rejection does not affect the ion release behavior of the device. Sterilization may be omitted if it can be demonstrated that prior sterilization has no effect on the ion release behavior of the device (**3**) and is not tested in media prone to microorganism growth.

9.1.1 Test specimens used for design parameter studies can be used, with the requirement that the metallurgical and surface conditions of the specimens are the same as the intended implantable medical device.

9.1.2 The number of samples tested should be justified. The devices should be selected such that they represent the worst case for releasable ions per unit surface area.

9.1.3 If, after testing clinical-quality product, additional understanding of the potential variations due to manufacturing is desired, test samples with varied manufacturing parameters (for example, during process validation) may be tested.

9.2 Loading, tracking, or deployment, or combinations thereof, of the test specimen, as it would occur clinically, should be simulated as closely as is reasonably possible, since these actions can potentially affect the overall ion release behavior of the material (a study concerning the impact of device loading on nickel ion release can be found in Ref **4**). A justification should be provided if preconditioning is omitted. See also Appendix X1 for rationale for preconditioning.

NOTE 8—As an example, for endovascular devices, testing should be performed after subjecting the device to preconditioning, which includes tracking and deployment of the device through an in-vitro fixture that mimics in-vivo anatomic conditions and deployment in deionized water at 37 °C ± 2 °C (**5**). Non-endovascular medical devices may require other types of preconditioning.

10. Procedure for Test Preparation and Start of the Test

10.1 Before the test starts, various activities should be carried out, including cleaning of test containers (if not pre-cleaned), preparing the test and spike and recovery solutions (see Appendix X2), and sample preparation (including loading, tracking, or deployment, or combinations thereof, if warranted).

NOTE 9—A visual inspection step, outside of any normal Quality Assurance Inspection, can be done before testing, but poses the risk of additional contamination of samples.

10.1.1 The cleaning procedure should be designed to minimize contamination of the test solution from the container and all lab equipment coming into direct contact with it. An example of a cleaning procedure for containers made of borosilicate glass and other materials that can withstand direct exposure to nitric acid, is to fill the container with a nitric acid solution (50 mL concentrated (68 % to 70 %) nitric acid and 50 mL of deionized (DI) water in a 100 mL solution), store it for 10 min, empty it, and then rinse the container three times with DI water.

NOTE 10—Measure the pH of the final rinse to ensure that the pH is ±0.1 pH of the stock DI water. This will ensure minimal residual contamination by the nitric acid cleaning.

10.1.2 Prepare the specimen such that the portion exposed to the test solution is in the same metallurgical and surface condition as the implantable form of the medical device being studied, including simulated deployment if warranted.

10.1.3 Estimate the total surface area of interest exposed to the solution in order to determine the surface/volume ratio of the specimen during the test.

10.1.4 The detection limit, solubility limits, and the amount of solution needed to fully cover the device should be considered when calculating the required volume of test solution.

NOTE 11—For nickel, the Food and Drug Administration (FDA) recommends a surface-to-volume ratio of 0.1 cm^2/mL to 1 cm^2/mL, if the nickel released does not approach the solubility limit in the test solution and is sufficiently above the detection limit (**3**).

NOTE 12—It is advisable to ensure an adequate volume for the analysis after the test.

10.1.5 Preheat the water bath, heating chamber, or oven to 37 °C ± 2 °C.

10.1.6 Measure and record the pH of the solution.

NOTE 13—pH can play an important role in the ion release behavior of materials.

[5] *Reagent Chemicals, American Chemical Society Specifications*, American Chemical Society, Washington, DC. For suggestions on the testing of reagents not listed by the American Chemical Society, see *Analar Standards for Laboratory Chemicals*, BDH Ltd., Poole, Dorset, U.K., and the United States *Pharmacopeia and National Formulary*, U.S. Pharmacopeial Convention, Inc. (USPC), Rockville, MD.