Designation: F2847 – 10

Standard Practice for Reporting and Assessment of Residues on Single Use Implants[1]

This standard is issued under the fixed designation F2847; 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 practice is to describe how the cleanliness of single use implants as manufactured shall be reported. This practice proposes how to approach the identification of critical compounds and suggests different analytical methods.

1.2 The practice does not address substances which are intrinsic to the implant properties or design. In particular, it does not address substances released during implant resorption, implant coatings, or leachables by design.

1.3 This practice does not address the cleanliness of implants which are re-processed, re-cleaned after unpacking for re-use in the hospital or by the manufacturer.

1.4 This practice does not establish limit values for residues.

1.5 This practice suggests appropriate test methods for the general specification of residues and residue requirements of implants. This practice may also be used to characterize semi-finished components for implants.

1.6 The test methods suggested and described herein refer to established analytical methods and to existing standard methods for chemical, biochemical, or biological analysis.

1.7 This practice is intended solely to provide guidance regarding suitable test methods and reporting conventions for residues, which may or may not affect implant biocompatibility. This practice does not suggest or recommend test methods for biocompatibility, which may be found in Practice F748 or in ISO 10993-1.

1.8 *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 and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E996 Practice for Reporting Data in Auger Electron Spectroscopy and X-ray Photoelectron Spectroscopy

E1078 Guide for Specimen Preparation and Mounting in Surface Analysis

E1504 Practice for Reporting Mass Spectral Data in Secondary Ion Mass Spectrometry (SIMS)

E1635 Practice for Reporting Imaging Data in Secondary Ion Mass Spectrometry (SIMS)

E1829 Guide for Handling Specimens Prior to Surface Analysis

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

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

F1251 Terminology Relating to Polymeric Biomaterials in Medical and Surgical Devices (Withdrawn 2012)[3]

F1877 Practice for Characterization of Particles

F2459 Test Method for Extracting Residue from Metallic Medical Components and Quantifying via Gravimetric Analysis

F2809 Terminology Relating to Medical and Surgical Materials and Devices

G121 Practice for Preparation of Contaminated Test Coupons for the Evaluation of Cleaning Agents

G131 Practice for Cleaning of Materials and Components by Ultrasonic Techniques

G136 Practice for Determination of Soluble Residual Contaminants in Materials by Ultrasonic Extraction

2.2 *ISO Standards:*[4]

ISO 10993-1 Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing

ISO 10993-17 Biological Evaluation of Medical Devices—

[1] This practice 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] The last approved version of this historical standard is referenced on www.astm.org.

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

Part 17: Establishment of Allowable Limits for Leachable Substances

ISO 10993-18 Biological Evaluation of Medical Devices—Part 18: Chemical Characterization of Materials

ISO 11737-1 Sterilization of Medical Devices—Microbiological Methods—Part 1: Determination of a Population of Microorganisms on Products

2.3 *United States Pharmacopeia (USP) Document:*[5]

<85> Bacterial Endotoxin Test

2.4 *European Pharmacopoeia (PhEUR) Documents:*[6]

2.2.23 Atomic Absorption Spectrometry

2.2.24 Absorption Spectrophotometry, Infrared

2.2.25 Absorption Spectrophotometry, Ultraviolet and Visible

2.2.28 Gas Chromatography

2.2.29 Liquid Chromatography

2.2.43 Mass Spectrometry

2.2.44 Total Organic Carbon in Water for Pharmaceutical Use

2.2.48 Raman Spectrometry

2.2.55 Peptide Mapping

2.2.57 Inductively Coupled Plasma-Atomic Emission Spectrometry

2.2.58 Inductively Coupled Plasma-Mass Spectrometry

2.5 *Association for the Advancement of Medical Instrumentation (AAMI) Document:*[7]

AAMI ST72 Bacterial Endotoxins—Test Methodologies, Routine Monitoring, and Alternatives to Batch Testing

2.6 *Other References:*

FDA Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Device, 1987[8]

200.7 EPA Methodologies for ICP[9]

8270C EPA Methodologies for GC-MS[9]

3. Terminology

3.1 Unless provided otherwise in 3.2, terminology shall be in conformance with Terminology F1251 and with Terminology F2809.

3.2 *Definitions:*

3.2.1 *action value, n*—the amount(s) of substance(s) tolerated at the surface of an implant by the manufacturer before it will interfere with the manufacturing process.

3.2.2 *exhaustive extraction, n*—extraction until the cumulative residue change is analytically insignificant or less than 10 % of the initial extract.

3.2.3 *limit value, n*—the maximum allowable amount(s) of substance(s) at the surface of an implant not yet found to be harmful for the surrounding tissues and organs. Its value is established and defined by the manufacturer.

3.2.4 *model residue, n*—a single substance or a mixture of substances that reflect the process materials likely to be encountered and used during the manufacturing of the device.

3.2.5 *residue, n*—a substance present at the surface of an implant or embedded therein that is not explicitly recognized and defined as part of the implant specification (special definition for residue analysis of surfaces). It includes process-based residues as well as contamination by environmental factors (adsorbates).

3.2.6 *single use implant, n*—a medical device which intended use is to be implanted permanently and that is not re-cleaned or re-worked for a second implantation after eventual removal.

3.2.7 *soiling, n*—procedure of applying known amounts of a substance onto a medical device for determination of process capability, that is, cleaning efficiency and extraction yields.

3.2.8 *spiking, n*—procedure of applying exact quantities of a substance to an analyte for instrumental calibration and determination reaction yield.

3.2.9 *surface area, n*—the projected surface area of a part. This area does not include the internal porosity of parts with cancellous, porous, or wire structure. It does include factors that correct for the estimated surface roughness.

4. Summary of Practice

4.1 This practice describes how to report residues on implant surfaces and indicates useful and typical applicable analytical methods.

4.2 Application of the test methods contained within this practice does not guarantee clinical success of a finished implant, but it will help to ensure consistency in its cleanliness.

5. Significance and Use

5.1 The quality and consequently the clinical performance of implants may be affected by residues. Residues may induce no tissue response, minor tissue irritations, or they may lead to local inflammation of tissues surrounding the implant which may lead to failure in short-term or long-term use. Residues may also cause harm at locations away from the implant. Residues may originate from manufacturing materials used in the course of processing, or may be the result of handling and packaging (**1-3**).[10]

5.2 This practice shall be used to report the results of testing for residue. All residues cannot necessarily be detected. It suggests standard techniques that may be applied for analysis, and provides suggestions for how limit values may be set.

[5] Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

[6] Available from European Directorate for the Quality of Medicines and HealthCare (EDQM), 7 allee Kastner, CS 30026, F67081, Strasbourg, France, http://www.edqm.eu/en/News-and-General-Information-43.html.

[7] Available from Association for the Advancement of Medical Instrumentation (AAMI), 4301 North Fairfax Drive, Suite 301, Arlington, VA 22203, http://www.aami.org.

[8] Available from Food and Drug Administration (FDA), 5600 Fishers Ln., Rockville, MD 20857, http://www.fda.gov.

[9] Available from United States Environmental Protection Agency (EPA), Ariel Rios Bldg., 1200 Pennsylvania Ave., NW, Washington, DC 20460, http://www.epa.gov.

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

5.3 Residues may be of inorganic, organic, or biological nature. They may exhibit as surface bound substance, or as an adsorbate (for example, electrostatically held), an efflorescence, or a mechanically held substance. Residues may be soluble in aqueous media, soluble in organic solvents, or may be insoluble particulates.

5.4 Data generated in validation processes, that is, cleaning validation or sterility validation may be used as results or as basis for setting acceptance criteria in the report.

6. Reporting of Residues on Implants

6.1 The reporting of cleanliness of implants shall include a table that lists at least sections on *(1)* the chemical categories, *(2)* the results of validation studies or of routine analysis, *(3)* the acceptance criteria if applicable, *(4)* the detection limits of the methods used, and *(5)* the methods of analysis (see Table 1).

6.2 *Categories of Residues:*

6.2.1 Residues shall be classified, as needed, according to the common description and reported accordingly as (I) inorganic, (II) organic, (III) biologic, (IV) microbiological, and (V) particulate residues.

6.2.2 In this practice, inorganic residues are referred to as substances of all elements with the exception of carbon-containing substances. Carbonates, graphite or graphite-like structures (for example, diamond like coatings) are traditionally listed as inorganic substances.

6.2.3 In this practice, organic residues are referred to as synthetic and natural carbon-based substances. It includes both small molecules with low molecular mass (for example, paraffin or low viscosity oil) and high molecular mass based synthetic polymers. Polysilanes and -oxanes are also considered organic residues.

6.2.3.1 In this practice, microbiologic residues are to be listed separately and differentiated as bioburden and endotoxin. It should be noted that for medical devices sold sterile, bioburden testing is often part of sterilization validation and is monitored on a predetermined schedule for the purpose of dose audits or process control.

6.2.4 In this practice, particulate residues are referred to as material insoluble in aqueous media or organic solvent, which can be removed from the surface of an implant by physical-chemical means without interfering with the integrity of the implant surface. Even though particulates shall be reported separately, they belong to one of the chemical classes mentioned above.

6.3 *Reported Units:*

6.3.1 Results of inorganic and organic analysis shall be reported as mass per implant and/or mass per surface area (use SI units).

6.3.2 Results of biological analysis shall be reported in the specific units per implant, that is, enumeration methods such as colony forming unit (CFU), or enzymatic assays such as for example, endotoxin units (EU).

6.3.3 Results of particulate analysis shall be reported in mass per implant, mass per surface area, number per device, number per surface area, or atomic-%, or fraction per surface area. The size range of particulates considered in the analysis (for example, based on filter pore sizes, capillaries, diffraction settings) shall be reported.

6.3.4 Results of surface analysis shall be reported as atomic-%, molecular-%, or fraction per surface area.

6.4 *Identification of Residues*—Residues that have been identified shall be listed separately in the report if they are considered significant by the practitioner of this practice.

TABLE 1 Suggested Table for Reporting of Residues

NOTE 1—The reported table shall reflect the mean value of all measurements of a product and the error including the error of the method.

NOTE 2—The column Applied Analytical Method exemplifies methods and applicable standards. They can be replaced by any method/standard protocol suitable for the particular residues.

Categories	Results of Analysis	Set Limit Values	Detection Limit	Applied Analytical Methods
Inorganic	[mass/implant] [mass/surface area]	[mass/implant] [mass/surface area]	[mass/implant] [mass/surface area]	ICP-OES (PhEur 2.2.57)
Organic				GC-MS (PhEur 2.2.28, EPA 8270C)
Biological				e-spray MS (PhEur 2.2.43)
Bioburden	[CFU/implant]	[CFU/implant]	[CFU/implant]	ISO 11737-1
Endotoxin	[EU/implant]	EU/implant[A]	[EU/implant]	USP<85> AAMI ST72
Particulate	[mass/implant] [mass/surface area] [Number/implant] or [cm^2/cm^2] [Atomic-%] or [Molecular-%]	[mass/implant] [mass/surface area] [Number/ implant] or [cm^2/cm^2] [Atomic-%] or [Molecular-%]	[mass/implant] [mass/surface area] [Number/implant] or [cm^2/cm^2] [Atomic-%] or [Molecular-%]	SEM (internal protocol) XPS (ASTM E996)
Visual Inspection	[Optical observations]	[Optical observations]	[Optical observations]	(internal protocol)

[A] Limit value as defined for device types listed in FDA Guidance for Industry and Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Text for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices (December 1987).

7. Quality Assurance

7.1 The cleanliness of the implant shall be determined using the final product after packaging. Assessment can also be performed at various stages along the manufacturing process for manufacturing control or validation.

NOTE 1—Sterilization processes can affect the chemical and biological nature of residues. The manufacturer may elect to assess the residue content before and after sterilization. In the case of bioburden, testing has to be performed before sterilization.

7.2 Each method of analysis shall be validated individually in the laboratory conducting the analysis.

7.3 The manufacturing process for the implant being analyzed shall be reviewed regarding manufacturing materials used, for example, lubricants, emulsions, buffing compounds, grit blast media, detergents, etc. The listing of all manufacturing materials will help to identify the appropriate analytical methods and facilitate toxicological and risk assessments.

7.4 It is recommended that analytical protocols be validated directly on the implant or on test coupons with similar material and surface properties by soiling with known amounts of manufacturing materials under conditions occurring in the implant processing. When working with model residues for soiling, it is important to assure that no unwanted chemical cross reactions occur. The use of spikes in eluates for quality control reasons should be also considered with certain test methods (**4**, **5**).

7.4.1 Worst-case implants or test coupons (regarding surface texture, machined features) and soiling with identified worst case manufacturing materials may be used to reduce the number of process analyses.

7.4.2 Protocols shall be validated for surface texture(s) and material(s) being analyzed.

7.4.3 Worst cast soiling compounds or model residues shall be relevant regarding composition, amount applied, and incubation conditions. A detailed procedure for preparing test coupons is found in Practice G121.

7.5 In case of extraction protocols, validation shall include the determination of recovery yields and the resulting accuracy of the method and the acceptance criteria for successful testing.

7.6 Each method of analysis shall be established with detection and quantification limits.

7.7 Reports shall include the analytical laboratory, the analyst performing the test, protocol specifics (where more than one option is possible in a standard method), and any modifications from the standard protocol.

8. Limit Values

8.1 Determination of company internal acceptance criteria for residues is required for quality assurance and review by regulatory authorities. A risk-based approach is appropriate for considering where and how residues can be introduced and the impact of existing controls such as validated cleaning and passivation processes.

8.2 The set value for a limit value be may be derived from historical and clinical analytical data, experience with the particular device or analogous devices, toxicological assessment based on acute local tissue reactions, or from data as specified in other standards and guidance documents.

8.3 Guides such as ISO 10993-17 may be helpful in establishing limit values. Calculation of limit values based on classical toxicological calculations (TE, NOEL, dose base on body mass and exposure times) requires special attention. Caution is advised in the use of such values since the assessment is based on the whole organisms and not on the local effect that define the fate of the implant.

8.4 The quantitative and qualitative rationales for the extrapolation or derivation of limit values shall be clearly documented.

8.5 The limit value reflects a maximum number that is not to be exceeded in any case. It is not a mean value of separate analyses, but it may be the value of a test group containing several devices in a single analysis.

9. Keywords

9.1 analysis; cleanliness; contamination; limit value; residues

ANNEX

(Mandatory Information)

A1. RESIDUE ANALYSIS

A1.1 The cleanliness of implants may be decisive for implant performance. An implant is exposed to many residue sources during manufacturing; some of the residues are potentially harmful for the patient health, some are not affecting the implant performance at all. Therefore it is important that the implant manufacturers are aware of the potential risks, take precautions, and use only validated manufacturing processes. Process and method validation includes many aspects, including choice of appropriate analytical methods, sample preparation, setting acceptance criteria, or setting sensitivity limits, respectively. The following sections describe and outline the most important considerations to be taken into account.