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.

A1.2 *Decision Tree for Sample Preparation and Analysis*—See Fig. A1.1.

A1.3 *Sample Preparation*:

A1.3.1 The following section describes a rational approach for selecting or developing methods for sample preparation and analysis. The typical steps are depicted in Fig. A1.1. However, the required procedures may vary dependent on the medical device. The choice of each analytical method and sample preparation procedure shall be justified and validated for each class of residues.

A1.3.2 Analysis can be performed locally (*in-situ*) or it can be performed on an extract solution. The decision on the appropriate approach to use depends on the medical device and shall be justified. Depending on the situation, each approach may offer some advantage over the others.

A1.3.3 *Preparation for Local in situ Residue Analysis:*

A1.3.3.1 The handling and preparation of specimens for direct surface analysis requires special attention. A guide on proper handling is for example found in Guides E1829 and E1078.

A1.3.4 *Preparation for Eluates by Extraction:*

A1.3.4.1 When applying extraction methods, established extraction protocols shall be applied to ensure the highest possible efficacy of residue recovery.

A1.3.4.2 Extraction is very complicated process that requires adaptation for each situation. The variables include

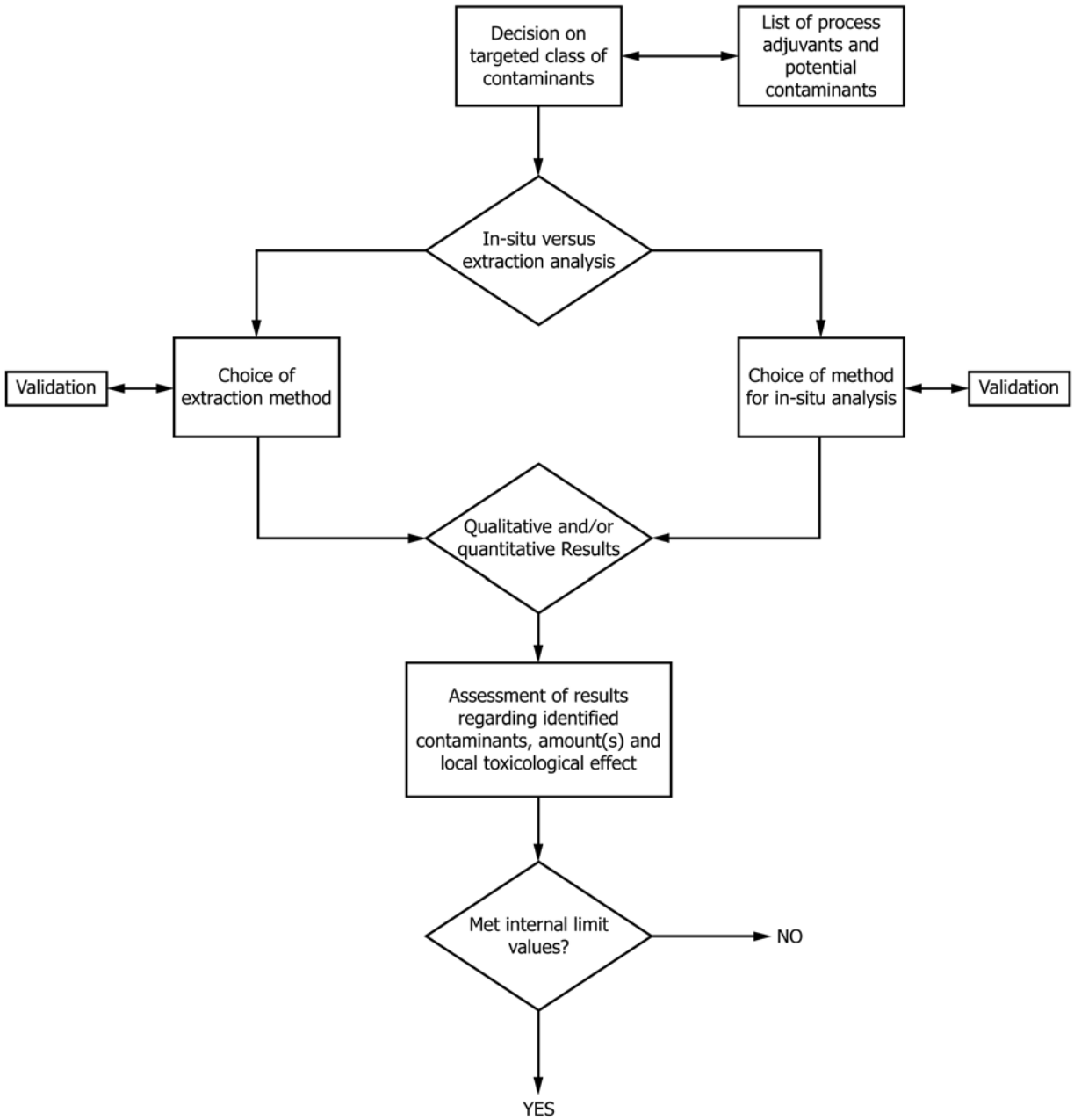

FIG. A1.1 Decision Tree for Sample Preparation and Analysis

choice of solvents, time, temperature, surface/volume ratio and mechanical force. It may be essential to test several conditions to establish suitable extraction efficiency. The extraction efficiency should exceed 75 % when possible. The use of mechanical force, that is, ultrasound, is highly recommended to detach residues from the surface. A practice for ultrasonic cleaning is found in Test Method F2459, and Practices G131 and G136.

A1.3.4.3 The extraction shall not interfere with the integrity of the medical device material, nor shall it cause elution of bulk components.

A1.3.4.4 Alternatively, surface etching procedures may be applied to remove strongly bound residues or material that was incorporated into the surface while processing.

A1.3.4.5 Particulates may be separated from extraction fluids by centrifugation or filtration using the protocols in Section 10 of Practice F561. These protocols can also be used for preparation of particulates for examination by SEM and EDXA.

A1.4 *Localized in situ Analysis*:

A1.4.1 In general, localized *in-situ* analysis may be applied for all classes of residues.

A1.4.2 Localized *in situ* analysis shall be performed to meet concerns regarding all residues can be removed by exhaustive extraction (for example, surface embedded blasting particles), or for validation of extraction protocols.

A1.4.3 It is strongly suggested that the analysis is performed at several locations on the device surface in order to meet concerns regarding the limited significance of spot analysis.

A1.4.4 Due to the variety of the implantable devices, the final decision on which *in-situ* methods shall be applied for the different classes of residues should be made by the manufacturer's specialists or expert advisors. A list of recommended methods and their application is found in Appendix X1.

A1.5 *Analysis of Eluates*:

A1.5.1 Eluates may be analyzed with a vast array of analytical methods. The eluates may be concentrated to increase the sensitivity of the methods for example, by evaporation, solvent exchange, etc. It must be ensured that the yield of the concentration method is known and that the extracted residues do not degrade, react or volatize while processing.

A1.5.2 Aqueous eluates may be analyzed for inorganic, organic, biological and particulate residues.

A1.5.3 Organic eluates are typically analyzed for organic and particulate residues.

A1.5.4 The analysis of particulate residues is described in the standards Test Method F2459. Particulate morphology may be characterized according to Practice F1877.

A1.5.5 Due to the variety of implantable devices, the final decision on which analytical methods shall be applied for the different classes of residues should be made by the manufacturer's specialists or expert advisors. A list of recommended methods and their application is found in Appendix X1 or in ISO 10993-18.

APPENDIX

(Nonmandatory Information)

X1. SPECIAL CHARACTERISTIC OF ANALYTICAL METHODS

TABLE X1.1 Analytic Methods and Use—Non-exhaustive

NOTE 1—Methods in bold are described briefly in subsequent paragraphs.

NOTE 2—Some of the listed methods allow only for quantification of residues. The identification of residues requires often the combination of several analytical methods.

NOTE 3—Some more detailed information on different approaches and test methods is found in literature (**1**, **3-10**).

Method(s)	Recommended for:				Suggested Standards
	Organics	Inorganics	Particulates	Biologics	
GC-MS/GC-TOF	X				PhEur 2.2.28/2.2.44
TOC	X				PhEur 2.2.44
RAMAN	X	X		X	PhEur 2.2.48
FTIR	X	X		X	PhEur 2.2.24
UV/Vis	X	X		X	PhEur 2.2.25
ICP-OES/ICP-MS		X			EPA 200.7 PhEur 2.2.57 PhEur 2.2.58
HPLC	X			X	PhEur 2.2.29
AAS		X			PhEur 2.2.23
EDS / EDXA		X	X		
Bioburden				X	ISO 11737-1
Endotoxin				X	USP<85> AAMI ST72
SEM			X		
Auger (AES)		X	X		ASTM E996
XPS (ESCA)	X	X	X		ASTM E996
TOF-SIMS	X	X	X		ASTM E1504
Optical Inspection	X	X	X		
Gravimetric	X	X	X		ASTM F2459
Peptides				X	PhEur 2.2.55

X1.1 *Inductively Coupled Plasma Optical Emission Spectroscopy or Atomic Emission Spectroscopy (ICP-OES/ICP-AES)*:

X1.1.1 ICP-OES is used to quantitatively determine the elemental composition of a material. It does not provide information about molecular groups. In ICP/OES, the sample is usually first prepared with heat, acids, or microwave digestion, or by laser ablation to convert it into an aerosol or gas. The gas is then atomized with a plasma. The resultant atoms are further energized by the plasma, and emit light at specific wavelengths. A diffraction grating separates the emitted light by wavelength, and detectors quantify the number of atoms of a specific element based on the amount of emitted light at a specific wavelength. The resolution of ICP-OES depends on the elements detected, and is typically around 2 ppb.

X1.1.2 Mass spectroscopy (MS) may be used as an alternative detection method. The sensitivity of ICP-MS may be up to 1 to 2 order of magnitude higher than that of OES.

X1.2 *Atomic Absorption Spectroscopy (AAS)*:

X1.2.1 Atomic-absorption spectroscopy (AAS) uses the absorption of light to measure the concentration of atoms in a gas phase. Similar to ICP-OES, it does not provide information about molecular groups. In AAS, the sample is passed into a flame or graphite furnace, which volatilizes any solvent, ashes organic matter, and vaporizes the analyte atom. Depending on the heating system, one can examine solutions, slurries, solids and particulates with AA. The atoms are then exposed to a light source, typically a hollow cathode lamp, although UV or laser sources have been used. In order to quantify a specific element, the same type of element must be used in the hollow cathode lamp. The energized electrons make transitions to higher electronic energy levels as they absorb light at their specific frequencies. The concentration of the specific atom is determined from the amount of absorption using a monochromatic detector. The sensitivity of AA can range down to 1 ppb.

X1.3 *FTIR/RAMAN Spectroscopy* :

X1.3.1 In Fourier transform infrared spectroscopy (FTIR), the infrared beam stimulates vibrations of chemical bonds at specific frequencies, and measures the absorption of the beam at those specific frequencies. The degree of absorption provides a measure of the concentration of specific chemical groups in a material or a combination of materials, and the frequency of the absorption peak helps to identify the chemical bond. Although the sensitivity depends on the type of material, FTIR can detect residues down to concentration of approximately 10 ppm. FTIR can be used for organic, inorganic, and

biological compounds. For example, FTIR is used to detect silica in industrial filters.[11] Particulate samples can be embedded in KBr or Nujol oil for identification via FTIR as well. Raman Spectroscopy operates similarly to FTIR, with the exception that instead of monitoring the absorption of infrared light at specific frequencies, one monitors the intensity of scattered photons, and the reduction in their vibration energy, which interact with molecular groups in the sample. The shift in vibrational energy helps to identify the molecular group, and the change in their intensity is related to the concentration of the molecular groups. Typical Raman systems can detect molecular groups down to 1 ppm, although more sensitive systems are available. Raman can be used on organic, inorganic, biological, and particulate matter.

X1.4 *Energy Dispersive X-ray Spectroscopy (EDS/EDX/EDXA)*:

X1.4.1 EDS is another technique to measure elemental information about a residue. Similar to other elemental techniques, it does not provide information about molecular groups. In EDS, an electron or photon beam is aimed down into the sample to be characterized. The incident beam excites an electron in an inner orbital of the sample prompting its ejection and resulting in the formation of an electron hole within the atom's electronic structure. An electron from an outer, higher-energy shell then fills the hole, and the excess energy of that electron is released in the form of an X-ray photons with an energy level specific to an individual element. A detector monitors the number of X-rays photons emitted at each energy level. EDS detectors are often used in scanning electron microscopy, which provides the incident electrons. EDS can detect materials down to concentrations of approximately 0.1 %. It can be used in a spectroscopic manner or in image mode. It must be mentioned though that the sampling depth of EDS is typically several microns, which lowers the sensitivity of detection of surface-bound residues. Quantification of materials requires a flat, smooth sample surface, in order to prevent spurious scattering of X-rays. EDS can be used on organic, inorganic, biological, and particulate matter.

X1.5 *X-ray Photoelectron Spectroscopy (XPS/ESCA)*:

X1.5.1 In XPS, electrons of atoms are excited so strongly with x-rays that the electrons of the outer shells leave their atom and eventually the sample surface as well if they originate from atoms close to the sample surface. The energy of the released photoelectrons is analyzed and allows for calculation of the binding energies in the atoms. This permits one to determine qualitatively the elements and their binding states as well as the quantitative composition. Since the information originates from atoms of the uttermost 4 to 6 nm of a sample surface that technique is method of choice for analysis minute amounts of residues.

X1.5.2 The method allows for analysis of all elements in the periodic table from Lithium to Uranium. Typically, the detection limit of the elements is 0.1 atom%, though, the sensitivity towards specific elements may vary. Special considerations have to be made in sample preparation and handling since the technique is extremely sensitive to residues. A Guide for Specimen Preparation and Mounting in Surface Analysis is found in Guide E1078. It is recommended to report the data according to Practice E996.

X1.6 *Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS)*:

X1.6.1 In TOF-SIMS, whole molecules, molecule fragments, or ions are desorbed from the top-most surface (single molecular layer) by an ion source. Subsequently, these ionized molecules, fragments, or ions are separated in a time of flight process and spectrometrically analyzed. TOF-SIMS is one of the most sensitive methods in surface analysis. Usually results are qualitative and allow for identification of residues. It may be used as a quantitative method if the residues are well known and the desorption and ionization process is studied in detail.

X1.6.2 It is recommended to report the analytical data according to Practice E1504 or Practice E1635.

X1.7 *Gravimetric Analysis of Extracts*:

X1.7.1 Gravimetric analysis is suitable for determination of all extractable residues including soluble and insoluble organic, inorganic, or biological material. This test method requires exhaustive extraction and use of a sonication technique is recommended to extract residue from the medical component. Other techniques, such as solvent reflux extraction may be used but have been shown to be less efficient in some tests. A detailed procedure is found in Test Method F2459.

X1.8 *Endotoxin*:

X1.8.1 The level of bacterial endotoxins shall be measured by a validated, compendial test method, such as USP <85>, or AAMI ST72. It is suggested to use a Limulus Amebocyte Lysate (LAL) or its biotechnological analogue based test for endotoxin determination. Detailed guidelines are found in the standard AAMI ST72 or in the 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.

X1.8.2 The analysis of cytokine expression as response to endotoxin may be used as an alternative, cell-based method. The profile of expressed cytokines varies with cell source. The method requires, however, analysis and comparison of more than one highly responsive cytokine and normalization to reporter molecules and compared to negative and positive controls.

X1.8.3 The extraction of endotoxin from medical device surfaces may be very difficult since endotoxin may exhibit a high affinity to material surfaces. Adaptation standard protocols may be required and therefore, it is recommended to verify the extraction process by soiling the sample with relevant amounts of endotoxin.

X1.9 *Total Organic Carbon (TOC)*:

X1.9.1 Total organic carbon (TOC) determination is an indirect measure of organic substances present in water. TOC

[11] http://www.cdc.gov/Niosh/nmam/pdfs/7602.pdf

analysis requires extracting the organic residues in ultra pure water. Special considerations are require to guarantee the solubility of the residues. A variety of acceptable methods is available for determining TOC.

X1.9.2 The various TOC apparatus have in common the objective of completely oxidizing the organic molecules in the sample water to produce carbon dioxide followed by measurement of the amount of carbon dioxide produced, the result being used to calculate the carbon concentration in the water. The protocols in-place have to differentiate between organic and inorganic carbon (carbonates), for example, by subtraction of reference measurements. The instrument has to be calibrated by substances that are expected to be easily and with difficulty oxidizable (for example, sucrose and 1,4-benzoquinone respectively). In addition standard curves are required for the process materials.

X1.9.3 The application of these methods is limited to processes that are well-defined since the sensitivity of the methods depends on the organic materials and may not be linear. Furthermore, results can not be related back to the amount of a residue—only total carbon.

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