Designation: F2212 – 19

Standard Guide for Characterization of Type I Collagen as Starting Material for Surgical Implants and Substrates for Tissue Engineered Medical Products (TEMPs)[1]

This standard is issued under the fixed designation F2212; 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.

INTRODUCTION

Collagen-based medical products are becoming more prevalent, especially in the area of soft tissue augmentation. The use of collagen in surgery dates back to the late 1800s, with the use of catgut sutures, human cadaveric skin, and fascia. More recently, collagen has been used in hemostatic sponges, dermal equivalents, injectables for soft tissue augmentation, as a matrix for cell-based products, and as a vehicle for drug delivery. It is because of the versatility of collagen in medical applications that specific characterizations should be performed as a way to compare materials.

1. Scope

1.1 This guide for characterizing collagen-containing biomaterials is intended to provide characteristics, properties, and test methods for use by producers, manufacturers, and researchers to more clearly identify the specific collagen materials used. With greater than 20 types of collagen and the different properties of each, a single document would be cumbersome. This guide will focus on the characterization of Type I collagen, which is the most abundant collagen in mammals, especially in skin and bone. Collagen isolated from these sources may contain other types of collagen, for example, Type III and Type V. This guide does not provide specific parameters for any collagen product or mix of products or the acceptability of those products for the intended use. The collagen may be from any source including, but not limited to, animal or cadaveric sources, human cell culture, or recombinant sources. The biological, immunological, or toxicological properties of the collagen may vary, depending on the source material. The properties of the collagen prepared from each of the above sources must be thoroughly investigated, as the changes in the collagen properties as a function of source materials is not thoroughly understood. This guide is intended to focus on purified Type I collagen as a starting material for surgical implants and substrates for tissue engineered medical products (TEMPs); some methods may not be applicable for gelatin or tissue implants. This guide may serve as a template for characterization of other types of collagen.

1.2 The biological response to collagen in soft tissue has been well documented by a history of clinical use (**1**, **2**)[2] and laboratory studies (**3**, **4**, **5**, **6**). Biocompatibility and appropriateness of use for a specific application(s) is the responsibility of the product manufacturer.

1.3 The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

1.4 **Warning—**Mercury has been designated by EPA and many state agencies as a hazardous material that can cause central nervous system, kidney, and liver damage. Mercury, or its vapor, may be hazardous to health and corrosive to materials. Caution should be taken when handling mercury and mercury-containing products. See the applicable product Material Safety Data Sheet (MSDS) for details and EPA's website (http://www.epa.gov/mercury/faq.htm) for additional information. Users should be aware that selling mercury or mercury-containing products, or both, in your state may be prohibited by state law.

1.5 The following precautionary caveat pertains only to the test method portion, Section 5, of this guide. *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] This guide is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.42 on Biomaterials and Biomolecules for TEMPs.

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

1.6 *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:*[3]

F619 Practice for Extraction of Medical Plastics

F720 Practice for Testing Guinea Pigs for Contact Allergens: Guinea Pig Maximization Test

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

F749 Practice for Evaluating Material Extracts by Intracutaneous Injection in the Rabbit

F756 Practice for Assessment of Hemolytic Properties of Materials

F763 Practice for Short-Term Screening of Implant Materials

F813 Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices

F895 Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity

F981 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Insertion into Bone

F1439 Guide for Performance of Lifetime Bioassay for the Tumorigenic Potential of Implant Materials

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

F1904 Practice for Testing the Biological Responses to Particles ***in vivo***

F2148 Practice for Evaluation of Delayed Contact Hypersensitivity Using the Murine Local Lymph Node Assay (LLNA)

2.2 *ISO Standards:*[4]

ISO 10993–1 Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing within a Risk Management Process

ISO 10993–9 Framework for Identification and Quantification of Potential Degradation Products

ISO 10993–10 Biological Evaluation of Medical Devices—Part 10: Tests for Irritation and Skin Sensitization

ISO 10993–17 Establishment of Allowable Limits for Leachable Substances Using Health-Based Risk Assessment

ISO 13408–1 Aseptic Processing of Health Care Products—Part 1: General Requirements

ISO 14971 Medical Devices—Application of Risk Management to Medical Devices

ISO 22442–1 Animal Tissues and their Derivatives Utilized in the Manufacture of Medical Devices—Part 1: Application of Risk Management

ISO 22442–2 Animal Tissues and their Derivatives Utilized in the Manufacture of Medical Devices—Part 2: Controls on Sourcing, Collection, and Handling

ISO 22442–3 Animal Tissues and their Derivatives Utilized in the Manufacture of Medical Devices—Part 3: Validation of the Elimination and/or Inactivation of Viruses and Transmissible Spongiform Encephalopathy (TSE) Agents

2.3 *U. S. and European Pharmacopeia Documents:*[5]

European Pharmacopeia 5.0

United States Pharmacopeia (USP), Edition XXX (30)

USP 30/NF 19 Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

2.4 *Code of Federal Regulations:*[6]

9 CFR 113 Standard Requirements

21 CFR 312 Investigational New Drug Application

21 CFR Part 820 Quality System Regulation

21 CFR Parts 207, 807, and 1271 Human Cells, Tissues and Cellular and Tissue-Based Products, Establishment Registration and Listing

21 CFR Part 1271, Part C Suitability Determination for Donors of Human Cell and Tissue-based Products, Proposed Rule

CFR 610.13(b) Rabbit Pyrogen Assay

Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products, Inspection and Enforcement. Proposed Rule. Federal Register/Vol. 66, No. 5/January 8, 2001/Proposed Rules, pp. 1552-1559

Guidance for Screening and Testing of Donors of Human Tissue Intended for Transplantation, Availability. Federal Register/Vol. 62, No. 145/July 29, 1997/Notices

Guidance for Industry and for FDA Reviewers, Medical Devices Containing Materials Derived from Animal Sources (Except for *In Vitro* Diagnostic Devices), November 6, 1998, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health

Federal Register Vol. 43, No. 141, Friday, July 21, 1978

Federal Register, Vol. 66, No. 13, Jan 19, 2001/Rules and Regulations, p. 5447

Federal Register, Vol. 72, No. 8, Jan. 12, 2007, pp. 1581–1619, Proposed Rule: Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants

2.5 *ICH Documents:*[7]

ICH M3(R2) Guidance for Industry M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials and

[3] 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.

[4] Available from International Organization for Standardization (ISO), ISO Central Secretariat, BIBC II, Chemin de Blandonnet 8, CP 401, 1214 Vernier, Geneva, Switzerland, http://www.iso.org.

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

[6] Available from U.S. Government Printing Office Superintendent of Documents, 732 N. Capitol St., NW, Mail Stop: SDE, Washington, DC 20401, http://www.access.gpo.gov.

[7] Available from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Secretariat, 9, chemin des Mines, P.O. Box 195, 1211 Geneva 20, Switzerland, http://www.ich.org.

Marketing Authorizations for Pharmaceuticals 62 FR 62922 (2009)

ICH S1A Guideline for Industry S1A The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals. 61 FR 8153 (1996)

ICH S1B Guidance for Industry S1B Testing for Carcinogenicity of Pharmaceuticals. 63 FR 8983 (1998)

ICH S1C Guideline for Industry S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals. 60 FR 11278 (1995)

ICH S1C(R) Guidance for Industry Addendum to Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addition of a Limit Dose and Related Notes. 62 FR 64259 (1997)

ICH S2A Guideline for Industry S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals. 61 FR 18199 (1996)

ICH S2B Guidance for Industry S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals 62 FR 62472 (1997)

ICH S5A Guideline for Industry S5A Detection of Toxicity to Reproduction for Medicinal Products. 59 FR 48746 (1994)

ICH S5B Guidance for Industry S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility. 61 FR 15360 (1996)

ICH Q1A(R2) Harmonized Tripartite Guideline for Stability Testing of New Drug Substances and Products (February 6, 2003)

2.6 *FDA Documents:*[8]

FDA Guidance for Industry, Pyrogen and Endotoxins Testing: Questions and Answers, June 2015, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Veterinary Medicine, Center for Devices and Radiological Health, Office of Regulatory Affairs

FDA Interim Guidance for Human and Veterinary Drug Products and Biologicals, Kinetic LAL Techniques, DHHS, July 15, 1991

U.S. Food and Drug Administration (FDA) and Committee for Proprietary Medicinal Products (CPMP), 1998 International Conference on Harmonization (ICH), Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin, Consensus Guideline ICH Viral Safety Document: Step 5

U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER), 1993 Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals

U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER), 1997 Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, 94D-0259

2.7 *AAMI Documents:*[9]

AAMI TIR 19:1998 Guidance for ANSI/AAMI/ISO 10993-7:1995, Biological Evaluation of Medical Devices—Part 7: Ethylene Oxide Sterilization Residuals

ANSI/AAMI/ISO 11737-1:2018 Sterilization of Healthcare Products—Microbiological Methods—Part 1: Determination of a Population of Microorganisms on Products

ANSI/AAMI/ISO 11737-2:2009 Sterilization of Medical Devices—Microbiological Methods—Part 2: Tests of Sterility Performed in the Definition, Validation and Maintenance of a Sterilization Process

ANSI/AAMI/ISO 14160:2011/(R) 2016 Sterilization of Health Care Products—Liquid Chemical Sterilizing Agents for Single-Use Medical Devices Utilizing Animal Tissues and Their Derivatives—Requirements for Characterization, Development, Validation and Routine Control of a Sterilization Process for Medical Devices

ANSI/AAMI ST67:2011/(R) 2017 Sterilization of Health Care Products—Requirements and Guidance for Selecting a Sterility Assurance Level (SAL) for Products Labeled "Sterile"

2.8 *Other References:*

Draft Guidance for Preclinical and Clinical Investigations of Urethral Bulking Agents Used in the Treatment of Urinary Incontinence, November 29, 1995. (ODE/DRARD/ULDB), Document No. 850[10]

Council Directive 93/42/EEC, with Respect to Medical Devices Using Tissues of Animal Origin[11]

Commission Directive 2003/32/EC, with Respect to Medical Devices Manufactured Using Tissues of Animal Origin[11]

EMEA/410/01-rev.2, Committee for Proprietary Medical Products, Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medical Products[12]

The European Agency for the Evaluation of Medicinal Products, (EMEA), Committee for Proprietary Medicinal Products (CPMP) Guidance Document for Decision Trees for the Selection of Sterilisation Methods (CPMP/QWP/054/98 corr 2000) and Annex to Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)[13]

3. Terminology

3.1 *Definitions:*

3.1.1 *adventitious agent, n*—an unintentionally introduced microbiological or other infectious contaminant.

[8] Available from U.S. Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993, http://www.fda.gov.

[9] Available from Association for the Advancement of Medical Instrumentation (AAMI), 4301 N. Fairfax Dr., Suite 301, Arlington, VA 22203-1633, http://www.aami.org.

[10] Available from U.S. Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993, http://www.fda.gov.

[11] Available from Office for Official Publications of the European Communities—European Law, 2, rue Mercier, L-2985, Luxembourg, http://eur-lex.europa.eu/en/'index.htm.

[12] Available from European Medicines Agency (EMEA), 7 Westferry Circus, Canary Wharf, London E14 4HB, U.K., http://www.eudora.org/emea.html, and http://www.emea.europa.eu/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf.

[13] Available from European Medicines Agency (EMEA), 7 Westferry Circus, Canary Wharf, London E14 4HB, U.K., http://www.eudora.org/emea.html, and http://www.emea.europa.eu/pdfs/human/qwp/005498en.pdf.