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FORT WAYNE METALS
Turning knowledge into solutions.

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Cytotoxicity and Biocompatibility of Medical Device Materials

Fort Wayne Metals Research Products Limited Liability Company, and its subsidiaries and affiliates (collectively referred to herein as "FWMRP,LLC") produce many different types of alloys and products that historically have been used for medical applications. The FDA provides a list of Recognized Consensus Standards, including materials. Both ASTM and ISO provide material standards for medical applications. However, the appropriateness of the material depends upon the application. FWMRP,LLC manufactures and sells material products which are used by its customers in the manufacture and sale of its products, medical devices or subcomponents of medical devices. The material products are manufactured by FWMRP,LLC pursuant to a written specification from the customer. The design of a medical device is the responsibility of the customer, not FWMRP,LLC. FWMRP,LLC does not guarantee, warrant or represent that the material product is biocompatible, and has undertaken no research or testing to determine the suitability of the material product for use in any customer product. It is the responsibility of the customer/company that proposes to put the medical device into commercial distribution to establish the appropriateness of the equipment, methods and materials used to manufacture the medical device as part of the process to obtain the authority to market the medical device.

Below are references which can be used to establish the appropriate methods for determination of the biological response to medical product designs and materials.

United States Food and Drug Administration (FDA)	www.FDA.gov
Center for Devices and Radiological Health (CDRH)	www.CDRH.gov
International Organization for Standardization (ISO)	www.ISO.org
American Society for Testing and Materials (ASTM)	www.ASTM.org

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ISO 10993-1:2003: Biological Evaluation of Medical Devices

ISO 10993 consists of the following parts, under the general title Biological Evaluation of Medical Devices:

- Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process
- Biological evaluation of medical devices -- Part 2: Animal welfare requirements
- Biological evaluation of medical devices -- Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- Biological evaluation of medical devices -- Part 4:Selection of tests for interactions with blood
- Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity
- Biological evaluation of medical devices -- Part 6: Tests for local effects after implantation
- Biological evaluation of medical devices -- Part 7: Ethylene oxide sterilization residuals

- Biological evaluation of medical devices -- Part 8: Selection and qualification of reference materials for biological tests
- Biological evaluation of medical devices -- Part 9: Framework for identification and quantification of potential degradation products
- Biological evaluation of medical devices -- Part 10: Tests for irritation and skin sensitization
- Biological evaluation of medical devices -- Part 11: Tests for systemic toxicity
- Biological evaluation of medical devices -- Part 12: Sample preparation and reference materials
- Biological evaluation of medical devices -- Part 13: Identification and quantification of degradation products from polymeric medical devices
- Biological evaluation of medical devices -- Part 14: Identification and quantification of degradation products from ceramics
- Biological evaluation of medical devices -- Part 15: Identification and quantification of degradation products from metals and alloys
- Biological evaluation of medical devices -- Part 16: Toxicokinetic study design for degradation products and leachables
- Biological evaluation of medical devices -- Part 17: Establishment of allowable limits for leachable substances
- Biological evaluation of medical devices -- Part 18: Chemical characterization of materials
- Biological evaluation of medical devices -- Part 19: Physico-chemical, morphological and topographical characterization of materials
- Biological evaluation of medical devices -- Part 20: Principles and methods for immunotoxicology testing of medical devices
- Biological evaluation of medical devices -- Part 22: Guidance on nanomaterials

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IS0 5832-1:1997(E): Implants for Surgery – Metallic Materials

IS0 5832 consists of the following parts, under the general title; Implants for Surgery – Metallic Materials:

- Implants for Surgery – Metallic Materials - Part 1: Wrought stainless steel
- Implants for Surgery – Metallic Materials - Part 2: Unalloyed titanium
- Implants for Surgery – Metallic Materials - Part 3: Wrought titanium 6-aluminium 4-vanadium alloy
- Implants for Surgery – Metallic Materials - Part 4: Cobalt-chromium-molybdenum casting alloy
- Implants for Surgery – Metallic Materials - Part 5: Wrought cobalt-chromium-tungsten-nickel alloy
- Implants for Surgery – Metallic Materials - Part 6: Wrought cobalt-nickel-chromium-molybdenum alloy
- Implants for Surgery – Metallic Materials - Part 7: Forgeable and cold-formed cobalt-chromium-nickel molybdenum-iron alloy
- Implants for Surgery – Metallic Materials - Part 8: Wrought cobalt-nickel-chromium-molybdenum-tungsten-iron alloy
- Implants for Surgery – Metallic Materials - Part 9: Wrought high nitrogen stainless steel
- Implants for Surgery – Metallic Materials - Part 10: Wrought titanium 5-aluminium 2.5-iron alloy
- Implants for Surgery – Metallic Materials - Part 11: Wrought titanium 6-aluminium 7-niobium

alloy
- Implants for Surgery – Metallic Materials - Part 12: Wrought cobalt-chromium-molybdenum alloy

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ASTM F981: Standard Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Bone

Control materials will consist of any one of the metal alloys in the referenced ASTM specifications F- 67, F-75, F-90, F-136, F-138, or F-562. See below.

Reference by Alloy:

Alloy Name(s): Titanium Grade(s) 1, 2, 3 & 4

ASTM F67, Standard Specification for Unalloyed Titanium, for Surgical Implant Applications (Grade 1 / UNS R50250, Grade 2 / UNS R50400, Grade 3 / UNS R50550, Grade 4 / UNS R50700)

ISO 5832-2 Unalloyed titanium

Alloy Name(s): CCM / Cast Cobalt - Chromium - Molybdenum Alloys

ASTM F75, Standard Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants (UNS R30075)

ISO 5832-4 Cobalt-chromium-molybdenum casting alloy

Alloy Name(s): L-605 / Vitallium

ASTM F90, Standard Specification for Wrought Cobalt-20Chromium-15Tungsten-10 Nickel Alloy for Surgical Implant Applications (UNS R30605)

ISO 5832-5 Wrought cobalt-chromium-tungsten-nickel alloy

Alloy Name(s): Ti-6Al-4V-ELI / Grade 23

ASTM F136, Standard Specification for Wrought Titanium-6Aluminum-4Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications (UNS R56401)

ISO 5832-3 Wrought titanium 6-aluminium 4-vanadium alloy

Alloy Name(s): 316L

ASTM F138, Standard Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Bar and Wire for Surgical Implants (UNS S31673)

ISO 5832-1 Wrought stainless steel

Alloy Name(s): MP35N® / 35N LT®

ASTM F562, Standard Specification for Wrought 35Cobalt-35Nickel-20Chromium-10Molybdenum Alloy for Surgical Implant Applications (UNS R30035)

ISO 5832-6 Wrought cobalt-nickel-chromium-molybdenum alloy

Additional alloys and specifications:

Alloy Name(s): Conichrome® / Elgiloy® (Grade 1) / Phynox® (Grade 2) / FWM®1058

ASTM F1058, Standard Specification for Wrought 40Cobalt-20Chromium-16Iron-15Nickel-7Molybdenum Alloy Wire and Strip for Surgical Implant Applications (UNS R30003 and UNS R30008)

ISO 5832-7 Forgeable and cold-formed cobalt-chromium-nickel molybdenum-iron alloy (except for Si.)

Alloy Name(s): 22-13-5

ASTM F1314 Standard Specification for Wrought Nitrogen Strengthened 22 Chromium – 13 Nickel–5 Manganese – 2.5 Molybdenum Stainless Steel Alloy Bar and Wire for Surgical Implants (UNS S20910)

Alloy Name(s): CCM

ASTM F1537, Standard Specification for Wrought Cobalt - 28Chromium - 6Molybdenum Alloys for Surgical Implants (UNS R31537 (Alloy 1), UNS R31538 (Alloy 2), and UNS R31539 (Alloy 3))

ISO 5832-4 Cobalt-chromium-molybdenum casting alloy / or ISO 5832-12 Wrought cobalt-chromium-molybdenum alloy

Alloy Name(s): Nitinol / Niti / 54.5 % to 57.0 % Nickel [Ni]

ASTM F2063, Standard Specification for Wrought Nickel-Titanium Shape Memory Alloys for Medical Devices and Surgical Implants

Alloy Name(s): Alloy 734

ASTM F1586 Standard Specification for Wrought Nitrogen Strengthened 21 Chromium—10 Nickel—3 Manganese—2.5 Molybdenum Stainless Steel Alloy Bar for Surgical Implants (UNS S31675)

Alloy Name(s): ASTM F899, Standard Specification for Stainless Steels for Surgical Instruments

Class 3—Austenitic Stainless Steel (301, 302, 303, 304, 316, 317…)
Class 4—Martensitic Stainless Steel (410, 416, 420, 431, 440…)
Class 5—Precipitation Hardening Stainless Steel (465, 630, 631, XM-16…)
Class 6—Ferritic Stainless Steel (430 F, XM-34…)

ISO 7153-1 Surgical Instruments - Metallic Materials - Part 1: Stainless Steel

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The FDA and the medical device regulatory agencies of other countries are utilizing consensus standards from a variety of organizations. For information about FDA's use of Standards, please see the CDRH Standards Program site.

American Association for the Advancement of Instrumentation (AAMI) A resource for national and international standards

American National Standards Institute (ANSI)
A private, nonprofit organization that administers and coordinates the U.S. voluntary standardization and conformity assessment system.

American Society for Testing and Materials (ASTM)
A non-profit organization that provides a global forum for the development and publication of voluntary consensus standards for materials, products, systems, and services.

International Electrotechnical Commission (IEC)
A global organization that prepares and publishes international standards for all electrical, electronic, and related technologies.

CENELEC Electronic Components Committee)
The European Committee for Electrotechnical Standardization

International Organization for Standardization (ISO)
A worldwide federation of national standard bodies from 140+ countries

NCCLS
A non-profit organization that develops standards and educational organization. NCCLS was formerly known as National Committee for Clinical Laboratory Standards. It is now a global organization and develops consensus documents for additional audiences beyond the clinical laboratory community.

Standards Information Program at the National Institute for Standards and Technology
Provides information on U.S., foreign, and international voluntary standards; government regulations; and rules of conformity assessment for non-agricultural products. The Center serves as a referral service and focal point in the U.S. for information about standards and standards related information. It also provides information regarding Technical Barriers to Trade (TBT)

The United States Pharmacopoeia (USP)
Publishes officially recognized standards for the use of medicines and other health care technologies

European Union Medical Device Regulation of 2017
European Union (“EU”) regulation governing the quality and safety of medical devices and accessories of medical devices for manufacturers, distributors, and/or importers of medical devices that are being placed, used or offered in the EU market.

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