Designation: ~~F2901 – 13~~ F2901 – 19

Standard Guide for Selecting Tests to Evaluate Potential Neurotoxicity of Medical Devices[1]

This standard is issued under the fixed designation F2901; 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 Medical devices may cause adverse effects on the structure and/or function of the nervous system. In this guide, these adverse effects are defined as neurotoxicity. This guide provides background information and recommendations on methods for neurotoxicity testing. This guide should be used with Practice F748, and may be helpful where neurotoxicity testing is needed to evaluate medical devices that contact central and/or peripheral nervous system tissue or cerebral spinal fluid (CSF).

NOTE 1—The results of these *in vitro* and *in vivo* tests may not correspond to actual human response.

1.2 *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~~ safety, health, and ~~health~~environmental practices and determine the applicability of regulatory limitations prior to use.*

1.3 *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]

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

F756 Practice for Assessment of Hemolytic Properties of Materials

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

2.2 *Other Referenced Documents:*

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

~~ISO/AAMI/ANSI~~ISO 10993-3 ~~:2003~~ Biological Evaluation of Medical Devices—Part 3: Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity[3]

~~ISO/AAMI/ANSI~~ISO 10993-5 ~~:2009~~ Biological Evaluation of Medical Devices—Part 5: Tests for In Vitro Cytotoxicity[3]

ISO 10993-6 Biological Evaluation of Medical Devices—Part 6: Tests for Local Effects After Implantation

ISO 10993–11 ~~:2006~~ Biological Evaluation of Medical Devices—Part 11: Tests for Systemic Toxicity

~~ISO/AAMI/ANSI~~ISO 10993-18 Biological Evaluation of Medical Devices—Part 18: Chemical Characterization of Materials[3]

~~ANSI/AAMI ST72~~ANSI/AAMI ST72 ~~:2010 Bacterial Endotoxins—Test~~ Bacterial Endotoxins—Test Methodologies, Routine Monitoring, and Alternatives to Batch Testing[3]

USP <151> Rabbit Pyrogen Test[4]

USP <161> Transfusion and Infusion Assemblies and Similar Medical Devices[4]

3. Summary of Guide

3.1 This is an informative guide and should be used with Practice F748.

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[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 F04.16 on Biocompatibility 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.

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

3.2 The duration of contact between the tissue and medical device should be considered when determining the appropriate panel of testing. This guide may not address neurosurgical instruments or medical devices that have transient incidental contact with the nervous system due to the limited tissue contact duration.

3.3 The evaluation of neurotoxicity should be considered in conjunction with material characterization and other information such as non-clinical tests, clinical studies, post-market experience, and intended use.

4. Significance and Use

4.1 The objective of this guide is to recommend a panel of biological tests that can be used in addition to the testing recommended in Practice F748. This guide is designed to detect neurotoxicity caused by medical devices that contact nervous tissue.

4.2 The testing recommendations should be considered for new materials, established materials with different manufacturing methods that could affect nervous tissue response, or materials used in new nervous tissue applications.

4.3 Chemical characterization can be used to evaluate similarity for materials with a history of clinical use in a similar nervous tissue application.

5. Terminology

5.1 *Definitions:*

5.1.1 *device-drug/biologic compatibility*—data demonstrating that drug, biologic and/or excipient and device materials are compatible if a specific drug or biologic is referenced in the device labeling.

5.1.2 *fluid path*—where fluids contact the channels in the device or component, and then the fluid enters the body.

6. Tests for Neurotoxicity

6.1 Testing should be performed on the final sterilized device, representative samples from the final sterilized device, or materials processed in the same manner as the final sterilized device. Representative samples should take into consideration all component materials that have direct or indirect tissue contact in appropriate ratios undergoing all the same manufacturing, cleaning, and sterilization processes as the final sterilized device. Testing of individual materials may be useful for research and development, but the definitive neurotoxicity evaluation should include all materials in the final version of the device. The test article should be exposed to all phases of manufacturing including processing, cleaning, sterilization, and packaging.

6.1.1 A complete description of all device materials and reagents used during manufacturing and processing should be provided with information on the source, purity, and toxicity profile. Chemical characterization studies can provide additional information on the device safety profile. See ~~ISO/AAMI/ANSI~~ISO 10993-18 for information on chemical characterization of materials.

6.2 The following tests should be considered to assess neurotoxicity of medical devices within the scope of this guide.

6.2.1 *Cytotoxicity*—Cytotoxicity assays are sensitive screening tools that generally serve as a starting point for evaluating medical device biocompatibility. See X1.4 for information on neuro-cytotoxicity testing.

6.2.2 *Genotoxicity*—Nervous tissue contains proliferating cell populations, and can respond to device implantation with a proliferative response. Nervous tissue is also known to give rise to various tumor types. To ensure that medical devices do not include genotoxic chemicals, the use of a panel of genotoxicity tests is recommended. The panel of genotoxicity tests should include a test for gene mutation in ~~bacteria,~~ bacteria and an in-vitro test with cytogenetic evaluation of chromosomal damage with mammalian cells or an in-vitro mouse lymphoma tk ~~assay, and~~ assay. Additionally, for devices containing novel materials an in-vivo test for chromosomal damage using rodent hematopoietic ~~cells. See ISO/AAMI/ANSI 10993-3~~ cells should be considered if the quantities of materials in the test extract following exhaustive extraction of the devices are above the threshold of detection of the in vivo assay. See ISO 10993-3 and the 2016 CDRH Biocompatibility Guidance (see X1.5) for additional information on genotoxicity testing.

6.2.3 *Implantation*—The use of a clinically relevant implantation study is recommended. The implantation site and animal model should be selected and justified according to the intended clinical use of the medical device. The ~~study should~~ test period should include an acute implantation period as well as other appropriate time intervals determined by the clinical exposure time, or go beyond the point where a tissue response steady state has been reached. The time course of the study should adequately characterize the response to implantation (e.g., absorbable dural substitute devices) and should be designed and justified based on the intended clinical use. The study should include both histopathology and neurobehavioral assessments. In addition to the use of hematoxylin and eosin ~~(H&E),~~ (H&E) which is a general morphological stain, more sensitive and specific histopathological assessments should be considered, including methods that are capable of enhancing and quantification of neurodegeneration, astrogliosis, microglia activation, and myelinopathy. See Polikov et al. (**1**)[5], Schmued et al. (**2**), and O'Callaghan et al. (**3**) and Bolon et al. (**4**) for examples of detection methods using Fluor-Jade for detection of neurodegeneration, glial fibrillary acidic protein (GFAP) for detection of astrogliosis, and Macrophage-1 antigen (MAC-1), Isolectin IB4, or ionized calcium binding

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