Designation: F3206 – 17

Standard Guide for Assessing Medical Device Cytocompatibility with Delivered Cellular Therapies[1]

This standard is issued under the fixed designation F3206; 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 This guide outlines the parameters to consider when designing in vitro tests to assess the potential impact of a delivery device on a cellular product being dispensed. This guide does not provide specific protocols, but rather suggests what should be considered the minimum characterization necessary to assess device cytocompatibility. Topics discussed include selecting an appropriate cell line(s), cell physiology parameters to measure, and relevant test procedure variables. Only cells suspended in liquid and infused through a device are considered. Cell therapies paired with scaffolds, suspended in hydrogels, or administered via other methods (e.g., tissue grafting) are not included in the scope of this document. This document does not address physical characterization of delivery devices, such as mechanics, composition, or degradation.

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 and health 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]

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

F2394 Guide for Measuring Securement of Balloon Expandable Vascular Stent Mounted on Delivery System

F2739 Guide for Quantifying Cell Viability within Biomaterial Scaffolds

F2809 Terminology Relating to Medical and Surgical Materials and Devices

2.2 *ISO Standard:*[3]

ISO 10993-5 Biological evaluation of medical devices – Part 5: Tests for *in vitro* cytotoxicity

3. Terminology

3.1 *Definitions:*

3.1.1 *cell line, n*—a generic term that includes primary, stem, and immortalized cells.

3.1.2 *cytocompatible, adj*—referring to the lack of unacceptable impact on a cellular product from interaction with a medical device used for delivery or interaction with manufacturing components. For example, a cytocompatible device does not unacceptably impact the cells passing through it as to compromise the potency of the cell therapy product.

3.1.3 *immortalized cell, n*—a primary cell that has been transformed or otherwise altered to provide an extended replication capacity beyond that of the originating primary cell. An immortalized cell may be naturally isolated (e.g., cancer cell) or purposely transformed in the laboratory.

3.1.4 *primary cell, n*—a cell with a finite replication potential that has not been biologically altered to promote extended survival. A primary cell may be frozen or freshly isolated but the passage history must be known and display demonstrable senescence.

3.1.5 *senescence, n*—the property attributable to finite cell cultures; namely, their inability to grow beyond a finite number of population doublings. **F2809**

3.1.6 *stem cells, n*—progenitor cells capable of self-replication, proliferation, and differentiation. **F2809**

3.1.7 *viable cell, n*—a cell capable of sustaining metabolic activity that is structurally intact with a functioning cell membrane. **F2739**

3.2 *Definitions of Terms Specific to This Standard:*

[1] This test method is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.43 on Cells and Tissue Engineered Constructs for TEMPs.

Current edition approved March 1, 2017. Published June 2017. DOI: 10.1520/F3206–17.

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

3.2.1 *ancillary equipment, n*—equipment to be paired with the delivery device (e.g., fittings, syringes, etc.) to facilitate in vitro testing through which the cells will pass but are not part of the delivery device as used in the clinic.

3.2.2 *delivery device, n*—a medical device designed to deliver therapeutic cells into the body.

4. Significance and Use

4.1 This guide is designed to assist medical device manufacturers as they develop new devices or qualify existing devices (e.g., catheters, needles) for delivering clinical cell therapies. Cytocompatibility considers the impact of the delivery device on the cells passing through the device during the delivery procedure. The biological safety of the device (e.g., the device's cytotoxicity) should be addressed via other methods, such as ISO 10993-5. It is understood that this guide does not address testing of specific cellular products with specific delivery devices. Such testing may be required by regulatory authorities prior to clinical trial of cellular product or marketing applications. This guide outlines considerations to make the product qualification procedures more likely to succeed and more cost effective.

4.2 The key aspects of assessing device cytocompatibility include selecting a test cell line or cell lines and determining the cell physiology parameters that will be measured to make a determination of cytocompatibility. Acceptance criteria for designating a device as cytocompatible are not detailed here. It will be up to the delivery device end user to determine if the results of a cytocompatibility assessment are sufficient to consider that device cytocompatible. Delivery device lot to lot variability may impact cytocompatibility, therefore validated manufacturing processes should be considered when producing devices for cytocompatibility assessments.

5. Cell Selection

5.1 The cellular response to delivery device contact will comprise the readout for the cytocompatibility characterizations considered in this guide. Given this, selection of the test cell line to be used is critical. Selecting a cell line that represents the intended use of the delivery device is encouraged, but not required. A single cell line or a panel of lines, whether stem cells, primary cells, immortalized cells, or a mixture thereof, may be necessary to characterize the device. Regardless of the approach selected, the cell line(s) chosen must demonstrate sensitivity to one or more evaluation parameters being used to characterize cytocompatibility. The identity of selected cell lines should be authenticated by appropriate means. Be mindful that some cell lines have licensing fees or patent protection which must be addressed. Also consider the available supply and potential issues with obtaining additional cell stocks which may introduce unacceptable variability. Ideally, as the field develops further, a reference cell line or panel of lines may be established for the purpose of device cytocompatibility testing.

5.2 It is critical that the chosen cells are well characterized. Cell and culture condition variables such as growth rate, handling protocols, media requirements, culture vessel coating, dissociation methods (if adherent), typical morphologies, stability during passaging, acceptable passage number, and similar parameters should all be well established. Delivered cells may be assayed for viability or function as part of the cytocompatibility evaluation. It is vital that the baseline viability and functionality of the cells is established and tracked over time in order to detect any adverse device impacts.

5.3 Animal cell lines may be a possibility for use in cytocompatibility testing; however, human cell data is preferable. Animal cells offer an advantage given that the *in vitro* testing can be supplemented by delivering cells directly into established animal models for further characterization; however, that is outside the scope of this guide.

6. Test Method Design

6.1 Determining the device impact on delivered cells necessitates careful characterization of the chosen cell line(s). The appropriate cell morphology and harvest density for use in an assay must be established. The potential impact of the dissociation method if using adherent cells (e.g., trypsin versus non-enzymatic dissociation) may also need to be considered. It is assumed that cells in culture will be used for purposes of expediency and throughput, but using freshly thawed cell aliquots to mimic a clinical application is also suitable. If this method is selected, the baseline physiology of the cells after thawing must be established. Consideration should be given to how the liquid chosen for suspension of the cells, or other suspension liquids, may interact with the delivery device materials (e.g., degrade the materials, extract leachables) and impact cytocompatibility.

6.2 Positive and negative assay controls will be included whenever possible. The negative control will be cells harvested and assayed having never touched the delivery device. Negative control cells should be prepared as if being passed through the device (e.g., at the set density, added to any ancillary equipment required). The positive control will be cells that show diminished viability and/or function. Producing a positive control can be accomplished by different approaches. A specific delivery device known to impair cells by impacting cell viability or function would be an ideal positive control. Alternatively, chemical or mechanical treatments known to impair cell line viability and/or function will suffice to demonstrate that the cell line is sensitive enough to report these aspects of physiology. Processing agents used in device manufacture or known to be present in the manufacturing environment may make suitable positive controls. If using chemical or mechanical treatments, a dose-response relationship should be evident to demonstrate the sensitivity of the chosen cell to impairment. Different treatments may be used on separate positive control samples in the same assay to perturb specific functions (i.e., multiple positive controls are acceptable).

6.3 A key aspect of testing will be selecting device delivery flow rates that approximate clinical use rates. At a minimum, delivery should be assessed at both a minimum and a maximum approximated clinical use flow rate. Syringe pumps or similar calibrated equipment should be used to ensure delivery consistency. Since the delivery flow rate will determine intradevice forces and the impact on delivered cells, when possible,