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Standard Guide for Assessment of Adventitious Agents in Tissue Engineered Medical Products (TEMPs)[1]

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1. Scope

1.1 This guide is intended as a resource for individuals and organizations involved in the production, delivery, and regulation of tissue engineered medical products (TEMPs). The safety from contamination by potentially infectious adventitious agents is important in the development of all TEMPs as well as their components. This guide addresses how to assess safety risks associated with adventitious agents and their byproducts. These agents currently include bacteria, fungi, mycoplasma, viruses, endotoxins, transmissible spongiform encephalopathies (TSEs), and parasitic organisms. This guide does not address TEMPs with live animal cells, tissues or organs, or human cells, including stem cells, grown on any animal feeder cells. Also excluded is patient follow-up testing.

1.2 This guide does not apply to any medical products of human origin regulated by the U.S. Food and Drug Administration under 21 CFR Parts 16 and 1270 and 21 CFR Parts 207, 807 and 1271. This guide does apply to cellular therapies regulated under the PHS (Public Health Service) act.

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 *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 to determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E1873 Guide for Detection of Nucleic Acid Sequences by the Polymerase Chain Reaction Technique

F2210 Guide for Processing Cells, Tissues, and Organs for Use in Tissue Engineered Medical Products

F2211 Classification for Tissue Engineered Medical Products (TEMPs)

F2312 Terminology Relating to Tissue Engineered Medical Products

F2386 Guide for Preservation of Tissue Engineered Medical Products (TEMPs)

2.2 *ANSI/AAMI Standard:*

ST72 Bacterial Endotoxin—Test Methodologies, Routine Monitoring and Alternatives to Batch Testing[3]

2.3 *Federal Regulations:*[4]

9 CFR Animals and Animal Products

21 CFR 210 Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs, General

21 CFR 211 Current Good Manufacturing Practice for Finished Pharmaceuticals

21 CFR 610.12 General Biological Products Standards—Sterility

21 CFR 610.13 (b) General Biological Products Standards—Purity Test for Pyrogenic Substances

21 CFR 820 Quality System Regulation

21 CFR 1270 Human Tissue Intended for Transplantation

21 CFR 1271 Human Cells, Tissues, and Cellular and Tissue-Based Products

2.4 *MDA Standard:*

Code of Practice for the Production of Human-Derived Therapeutic Products[5]

2.5 *U. S. Pharmacopeia Document:*

United States Pharmacopeia (USP), Edition XXIV (24)[6]

3. Terminology

3.1 *Definitions:*

[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 F04.45 on Adventitious Agents Safety.

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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. Government Printing Office Superintendent of Documents, 732 N. Capitol St., NW, Mail Stop: SDE, Washington, DC 20401, http://www.access.gpo.gov.

[5] Available from Medicines and Healthcare Products Regulatory Agency (MHRA), Hannibal House, Elephant & Castle, London SE1 6TQ, U.K.

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

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3.1.1 *adventitious agents, n*—unintentionally introduced microbiological or other infectious contaminant. In the production of TEMPs, these agents may be unintentionally introduced into the manufacturing process or into the final product or both. (See Terminology F2312.)

3.1.1.1 *Discussion*—In this guide, adventitious agents also include microbiological or other infectious contaminants that may be endogenous to the starting cells or tissue.

3.1.2 *endotoxin, n*—pyrogenic high molar mass lipopolysaccharide (LPS) complex associated with the cell wall of gram-negative bacteria.

3.1.2.1 *Discussion*—Though endotoxins are pyrogens, not all pyrogens are endotoxins. Endotoxins are specifically detected through a Limulus Amebocyte Lysate (LAL) test.

4. Significance and Use

4.1 TEMPs may be composed of biological products (for example, human cells, organs, tissues, derivatives, and processed biologics), biomaterials (for example, substrates and scaffolds composed of polymers or collagen), and biomolecules (for example, recombinant proteins, alginates, and hyaluronates) (see Terminology F2312). Those TEMPs that contain human viable cells, organs, or tissues differ in terms of adventitious agent safety from other TEMPs because of the need to preserve viability of the organ, tissue, or cellular components. The need for preservation of viability limits processing options for the reduction or elimination of adventitious agents. Examples of TEMPs are listed in Classification F2211.

4.2 To ensure production and use of TEMPs with minimal risks associated with microorganisms and other adventitious agents, a multi-tiered approach is required. Donor testing, as well as testing of components and raw materials by sufficiently sensitive assays that are state of the art is usually necessary. Compliance with good manufacturing practices (GMPs) and good tissue practices (GTPs), where applicable, is required (21 CFR 210, 211, 820, 1270, and 1271). Although some of the components of the TEMPs may be processed to remove potential microbiological contaminants, viable tissues and cellular components are generally unable to withstand rigorous processing without losing functionality. For those TEMPs containing tissues or cells for which banking is not possible, even greater reliance on donor screening, component testing, and manufacturing controls is required. When more upfront testing is possible, there is generally greater confidence in the safety of the final product. Process validation can enhance confidence in the ability of the TEMPs' producer to minimize risks from adventitious agents.

4.3 Throughout this guide, the reader is referred to other documents that may provide specific information that can be applied in the manufacture and testing of TEMPs. Although many of these documents were not written with TEMPs in mind, parts are often applicable. Most of the potentially applicable position papers and guidance documents from many regions of the world can be accessed via the internet. New documents are continually produced. The MDCA (U.K. Medical Devices Agency, now part of MHRA, Medicines and Healthcare Products Regulatory Agency) Code of Practice for the Production of Human-Derived Therapeutic Products provides information on quality control, microbiological safety of donations, production, and processing practices. Two Rijksinstituut voor Volksgezondheid en Milieu (RIVM) reports provide valuable information. One of these reports addresses preclinical safety assessment of TEMPs, and the other provides an approach to risk management for TEMPs (**1**, **2**).[7]

4.4 References may be made to draft guidances and rules. These should not be read as requirements.

5. Sources of Risk

5.1 *Donor*—In some cases, donors with potential previous exposure to certain infectious agents must be excluded. Guidance on donor selection is available from the American Association of Tissue Banks (AATB) and the U.K. Department of Health (**3**, **4**). The U.S. Food and Drug Administration (FDA) has produced many documents that provide useful information on donor testing (**5-11**). There may be specific requirements for different regions of the world. For TEMPs with autologous cells, donor testing is also recommended because of the potential for expansion of adventitious agents during manufacturing (**12**), and the potential for cross-contamination of other products manufactured concurrently in the same facility.

5.2 *Nonviable Animal Material*—The sponsor (product owner) has the responsibility to substantially reduce risks from adventitious agents, including TSEs, in nonviable animal materials. Mitigation of such risks can include scrutiny over donor sourcing or proven, rigorous processing, or both.

5.3 *Cell Banks*—Many TEMPs include cells that can be banked. Master Cell Banks (MCB) and Working Cell Banks (WCB) can be prepared and extensively tested for the presence of adventitious agents. Although TEMPs are not included in the scope of International Conference on Harmonization (ICH) guidelines, the ICH guideline on cell substrate characterization does provide useful information on the production, testing, and storage of cell banks (**13**). Further information may be found in an FDA publication on cell line characterization and the ICH guideline on viral safety (**14**, **15**).

5.4 *Raw Materials:*

5.4.1 The raw materials used in the manufacture of the cellular components of TEMPs are controlled by a number of requirements that describe the microbiological safety testing of components of cell culture media and reagents used in the manipulation of the cells during culture. Some of these materials are manufactured synthetically, for example, amino acid supplements of culture medium. Much more frequently, however, materials are of animal origin such as bovine serum (essential for many mammalian culture systems) or, in the case of anchorage-dependent cell lines, trypsin.

5.4.2 Raw materials of human and animal origin are of particular concern to the manufacturer and licensing authorities, owing to their potential contamination with extraneous agents from the source animal. Most manufacturers of

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

biotechnology-derived products do not themselves produce raw materials, but depend on external suppliers. A certificate of analysis indicating all tests performed, with results, and including data on the adventitious agent testing should also be obtained. A critical examination of the microbiological safety testing carried out by the supplier is recommended. As this may not be appropriate to satisfy the regulatory agencies, manufacturers may have to repeat and extend the adventitious agent testing performed by the supplier to ensure that raw materials meet the performance and safety requirements for the production process. Alternatively, it may be appropriate for the TEMPs manufacturer to demonstrate that their processing methods reduce the risk to an acceptable level. Tissue culture components are also discussed in Guide F2210.

5.4.3 Other raw materials should be tested to demonstrate they are free of adventitious agents. In some cases, the testing performed by the raw material supplier is sufficient. If a raw material is available only as research grade, then the sponsor should test that material for adventitious agents.

5.5 *Transport*—After packaging, the external surfaces of the containers may need to be decontaminated or cleaned or both. Container integrity and shipping validation are also important elements for ensuring TEMPs with a minimized defined risk from adventitious agent contamination are delivered to the handlers and users of the final products.

5.6 *Processing*—Adventitious agents can be introduced into the TEMPs during processing. The agents can be derived from contaminated environments, personnel, raw materials, and processing materials, including water, and cross-contamination from previously or concurrently processed products. Processing is addressed in detail later.

5.7 *Storage*—Adventitious agents can be introduced during the storage of all materials. Storage of the starting tissues or cells, raw materials, and final product requires a standardized procedure. The outer surface of the container may need to be decontaminated again prior to use.

6. Processing and Process Validation

6.1 Compliance with GMPs or GTPs, or both, when in effect, is essential for the production of TEMPs that have a minimized defined risk of transmitting adventitious agents. One of the major considerations is aseptic processing. Aseptic processing must be validated and then periodically revalidated to prevent contamination by microbial contamination. Refs (**16-18**) should be evaluated and applied to TEMPs, where feasible. Relevant elements are raw materials testing; suitable control of the processing environment and routine environmental monitoring; operator training; implemented documentation systems; use of suitable, validated analytical test methods; process design; equipment qualification and process validation; and container-closure system validation. Guide F2210, GMPs, and GTPs address many of these issues. Process design, equipment qualification, and process validation are discussed in the following sections.

6.2 *Process Design:*

6.2.1 Each step in the process should be evaluated for potential exposure to environmental contamination, including introduction of contamination by personnel. Processing materials, such as water and buffers, should be free from adventitious agents. Water quality should be evaluated. Depending on the intended use, either water for injection (WFI) or sterile purified water may be appropriate. To ensure further confidence in the process, where feasible, inactivation steps that are suitable for adventitious agents should be incorporated into the process, and decontamination and cleaning protocols established for any contact surfaces.

6.2.2 When multiple processing steps are used, storage conditions that protect the product intermediates from adventitious agents must be incorporated into the process scheme. When multiple products are being processed in the same environment, even more stringent environmental controls may need to be implemented. The use of disposable equipment may be advantageous for ensuring microbiological safety of the TEMPs, but that equipment must be suitably disposed of so that no other facilities or individuals are put at risk (**19**).

6.3 *Equipment Design and Qualification*—Where disposable equipment is not appropriate, equipment design should be considered to prevent contamination by adventitious agents. Dead legs, crevices, and threaded fittings are likely sites to harbor adventitious agents. Contact surfaces must be accessible and compatible with decontamination and cleaning agents. Equipment is qualified by performing a design qualification, an installation qualification, and an operational qualification. These qualification operations are defined in an ICH document on good manufacturing practices for active pharmaceutical ingredients (**20**).

6.4 *Use of Suitable, Validated Analytical Test Methods*—Processes cannot be validated without the use of validated assays. During development, those assays that provide the most relevant information should be established and validated. In some cases, the data from traditionally used assays for adventitious agents will not be available in time to release TEMPs containing viable cells for patient use. Other, more rapid assays may have to be validated against the traditional assays. Data from in-process testing are particularly useful for the manufacture of products containing viable cells since final product testing results may not all be available prior to product use. Appropriate in-process testing is strongly recommended for such products. For further guidance, see Reference (**21**).

6.5 *Process Validation Issues Relevant to Adventitious Agent and Contamination Control:*

6.5.1 In the case of cellular- and tissue-based TEMPs, it may be necessary to perform many more runs than the traditional three to five consecutive runs to ensure the process controls and outputs are sufficient to minimize the risks from adventitious agents and their byproducts. For TEMPs, the use of medium or a product reference standard may be the most logical approach to maintaining a validated state. Medium or the standard can be periodically run through the process to provide documented evidence that the process provides a product meeting specifications that are related to adventitious agent control.

6.5.2 Information on process validation can be found in several documents. FDA has published guides on general

principles of process validation and on validation of human tissue products (**22**, **23**). The ICH document on active pharmaceutical ingredients provides a good framework and defines qualification and validation activities. Two ICH guidelines provide information on validation of analytical methods (**24**, **25**).

6.5.3 Periodic revalidation of the process with the in-house reference standard or media will also provide some confidence in the capability of the process to provide TEMPs with minimized risk from adventitious agents. Whenever there are new reagents, new processes, process changes, new personnel, or other situations, such as an out-of-specification result, process validation should be repeated. If a reference standard is used, it should be properly stored and its stability validated.

6.5.4 The manufacturing process used will depend on the properties of the components and the requirements for the final TEMPs. There are a wide range of processes because of the variability in the sources and properties of different TEMPs and their components. However, in many cases, unit operations will consist of expansion of cells, removal of excess culture fluid, purification of scaffold, assembly of final product, packaging, and shipping. Each unit operation must be validated and appropriate validated in-process assays used, where feasible, to minimize risks from adventitious agents. Validated storage times and conditions must be used between each process step. The capability of antimicrobial preservatives to inhibit microbial growth should be validated along with the preservation process. If cryopreservation is used, it is important to protect the product from microbial contamination in the liquid nitrogen vessel. When feasible, products should be tested after thawing (**4**). The American Association of Tissue Banks (AATB) also provides guidance on storage (**26**).

6.5.5 Potential risks from cross-contamination by adventitious agents can be minimized by segregation of different products by time or space or both. Personnel and equipment should be dedicated to one product at a time. Closeout inventories and cleaning validation between products are important elements in the prevention of cross-contamination by potential adventitious agents.

6.5.6 Process validation should be performed for any inactivation or removal steps that minimize risks from adventitious agents and their byproducts. Spiking studies are often performed on a model system to demonstrate the effectiveness of inactivation or removal steps or both. Inactivation or removal of potential adventitious agents in viable tissue or cellular components of the TEMPs may not be possible.

6.5.7 Equipment cleaning and decontamination validation can, in some cases, be accomplished with a combination of the small-scale coupon studies (see 6.2.2) and in-process monitoring during the conformance batches. Data generated during validation should provide evidence that decontamination agents do not impair functionality of equipment. Routine monitoring should be continued after validation is complete.

6.6 *Container-Closure System Validation*—Validation of the container-closure system must also be performed. Details can be found in Refs (**27**, **28**). In most cases, TEMPs cannot be terminally sterilized.

6.7 *Preservation*—Preservation of TEMPs is addressed in Guide F2386.

7. Final Product

7.1 For the design of TEMPs with the lowest possible risks for disease transmission, it is a prerequisite that in addition to assessing the safety of the individual components and the processing procedures, the final product is also tested.

7.2 In many cases, traditional test methods will not be sufficiently rapid, and newer technologies will be used to release the product. In addition to adventitious agent testing, test methods may include assays for byproducts of adventitious agents, for example, endotoxin. Stability testing is also addressed by FDA and ICH documents, and part of a stability profile includes a demonstration that it remains uncontaminated by adventitious agents during its storage period (**29**, **30**).

7.3 In-process sterility testing at critical points during manufacturing of viable cellular products is useful when tests on the final product will not be available prior to use of the product in patients. For example, this might be done routinely during extended culture periods and after critical points in manufacturing, such as when cells have undergone activation or other modification. The results of this in-process testing should meet acceptance criteria as part of required final product specifications (**31**). When in process testing is used for product release, testing on the final product must also be performed, and a system put in place to report occurrences of sterility failure detected after product release.

7.4 Representative retention samples, where appropriate, should be maintained under appropriate conditions so that a thorough investigation can be performed in the event that an adverse patient reaction is observed. The size of a batch may be small for many TEMPs, particularly those containing autologous cells, but the TEMPs sponsor should ensure that adequate product is archived. Archival time should be established based on current regulatory expectations and functional lifetime or beyond, when feasible.

8. Adventitious Agents, Byproducts, and Detection Methods

8.1 In this section, an overview of potential adventitious agents and testing methods is presented (see Table 1). Fungi, bacteria, mycoplasma, viruses, TSEs, and parasites are included. Byproducts of some of these agents, for example, endotoxin or other pyrogenic material from bacteria, are also considered. The TEMPs' manufacturer should determine which, if any, of these agents should be tested for and where in the process that testing should occur. A risk assessment and discussions with relevant regulatory agencies should enable the manufacturer to make appropriate choices. Although the sections below provide examples of some newer test methods, it is important to realize that there is rapid progress in this field.

8.2 Knowing exactly which tests to perform can require significant expertise. Some tests are better suited to viable materials while others are more suitable for nonviable components of TEMPs. Since scientific progress is rapid in this field,

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