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Standard Guide for Determining the Impact of Extractables from Non-Metallic Materials on the Safety of Biotechnology Products[1]

This standard is issued under the fixed designation E 2097; 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 covers procedures and test methods for process component qualification by the end user. The goal is to assess the safety impact of extractables from non-metallic process components used in contact with bioprocessing solutions. This encompasses the impact of extractables on the safety of the final product as it passes through the various stages of the manufacturing process. This guide is not designed for evaluation of metallic materials, final product container/closures or those components intentionally added to the product or production streams during the manufacturing process. Testing of solids and extracts is specified in other ASTM standards. Materials must be qualified by specific use.

1.2 The values stated in SI units are to be regarded as the standard.

1.3 There is no companion guide available.

1.4 *Safety/Fire hazards*: Extractions with organic solvents will be infrequent under this Guide, but, when used must be treated as potential fire/explosion hazards.

1.5 *This guide 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.*

2. Referenced Documents

2.1 *ASTM Standards:* [2]

D 1203 Volatile Loss from Plastics Using Activated Carbon Methods

D 4754 Two-Sided Liquid Extraction of Plastic Materials Using FDA Migration Cell

D 4874 Leaching Solid Material in a Column Apparatus

D 4951 Determination of Additive Elements in Lubricating Oils by Inductively Coupled Plasma Atomic Emission Spectrometry

F 619 Standard Practice for Extraction of Medical Plastics

F 749 Evaluating Material Extracts by Intracutaneous Injection in the Rabbit

F 750 Evaluating Material Extracts by Systemic Injection in the Mouse

F 813 Direct Contact Cell Culture Evaluation of Materials for Medical Devices

F 895 Agar Diffusion Cell Culture Screening for Cytotoxicity

3. Terminology

3.1 See the Compilation of ASTM Standard Definitions. Review with the Terminology Committee, E48. See A7.2.1 for details of set up and Part E, Terminology in ASTM Standards.

3.2 *Definitions:*

3.2.1 *biopharmaceutical*—any drug product produced from living organisms.

3.2.2 *biotechnology solution*—a solution containing or producing products from living microbial, animal or plant cells or by the enzymes from those cells.

3.2.3 *biotechnology product*—a discrete chemical entity produced by growing single cell organisms with unique genetic information.

3.2.4 *elution cytotoxicity*—see USP.

3.2.5 *emission spectrographic analysis (ESA)*— an analytical technique for determining metals in a sample vaporized in a plasma arc.

3.2.6 *extractables*—residues from solid process components not intentionally part of the product process stream.

3.2.7 *fermentation*—the biochemical reaction process where microorganisms in a nutrient medium convert a feedstock to a product.

3.2.8 *inductively coupled plasma (ICP)*—an analytical technique designed to quantitate chemical elements.

3.2.9 *materials of construction*—high molecular weight or solid materials, used in biopharmaceutical process equipment which contact process solutions and can potentially release extractable residues.

[1] This guide is under the jurisdiction of ASTM Committee E48 on Biotechnology and is the direct responsibility of Subcommittee E48.03 on Unit Processes and Their Control.

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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.

3.2.10 *non-volatile residue (NVR)*—non-volatile material remaining after evaporating a solvent into which the residue has been extracted (See USP).

3.2.11 *oxidizable substances (OS)*—chemical compounds which may be oxidized by potassium permanganate under specified conditions (See USP).

3.2.12 *product contact material*—a material which physically contacts a solution containing the chemical entity designated the product.

3.2.13 *process materials*—high molecular weight or solid materials which contact process solutions potentially releasing extractable residues.

3.2.14 *purification*—the process by which the desired product is separated from the production process solution.

3.2.15 *residue on ignition (ROI)*—the residue remaining after ashing a material at high temperature.

3.2.16 *total organic carbon (TOC)*—an analytical technique for measuring the carbon associated with organic molecules in a solution.

4. Significance and Use

4.1 This guide applies to the determination of the safety of non-metallic materials used in contact with biotechnology product containing solutions. Process materials leach low level of residues into water, cell culture media, buffers, and other product containing solutions. This document offers guidance on determining the safety of these materials (process materials) for use. The goal is to prevent toxic extractables from entering process streams and ultimately contaminating the final product in unacceptable levels.

The purpose of this guide is to describe tests to qualify materials with respect to any extractable substances so as to prevent unintentional introduction of a potential source of objectionable substances. An extractable material is objectionable if it is toxic, interacts with product constituents, interferes with required assays, or otherwise affects the process stream so as to adversely affect critical quality parameters, for example, purity, safety, efficacy, identity, strength of the final product or its successful production. All organizations producing pharmaceutical products should consider the points in this guide when qualifying process materials for use in their production processes.

4.2 This guide outlines the application of the process material tests primarily in ASTM or USP. Typical process materials include high molecular weight polymers and solids such as hoses, filters, filter housings, containers, valve diaphragms, gaskets, o-rings, chromatography resins, and chromatographic columns.

4.3 The battery of tests described in this guide is intended to cover a wide variety of potential attributes of materials and to characterize possible extractables.

4.4 The material specification will vary depending on the impact on the final product and the point in the process that the product solution contacts the material. Tighter specifications should be considered for extractables for final product purification process materials than for fermentation media process materials.

5. Reagents

5.1 The quality of reagents used for the procedures indicated in this guide are specified in the test standards referenced (for example, ASTM and USP).

6. Procedure

6.1 During research and development to define the manufacturing process for a desired biotechnology product, select functional product contact materials predicted to be suitable based on manufacturer specifications. Choose materials which have specifications defined by pharmaceutical compendia to the extent possible. The goal is to find and use materials that will permit an acceptable level of extractables into the process solution. Materials should be approved by specific process use. A written protocol should be prepared outlining the tests to be done on each process material qualified. Qualified materials must be well defined and documented to assure equivalent replacements may be obtained. Vendor audits are necessary for all suppliers of product contact material with significant extractables.

When a high quality, functional material is identified, subject it to the following procedure as part of the validation of the process.

6.2 Choose the production function from Table 1. Use already validated ASTM or USP test methods wherever possible. If the product is to be licensed in a country with other compendial requirements, those will have to be considered as well. If test methods are the same but limits are different, use the more stringent limits.

NOTE 1—The cumulative effect of the ongoing removal of extractables can potentially affect the performance of plastics in certain applications.

6.3 Perform the tests designated in Table 1. Where extractions are done, follow Practice F 619-79 (1991) . Increase the time, temperature and concentration of the extraction several fold beyond production conditions to build in safety factors and insure worst case. Also it may be appropriate to exacerbate other factors affecting the extraction capability of the solvent such as organic concentration and pH. Demonstration of depletion of extractable material can be shown by repeated extraction and testing for non-volatile residue or oxidizable substances.

6.4 Characterize the product contact process material by through the film, pyrolysis, attenuated total reflectance or solution infrared methods. The infrared scan will become the reference for subsequent lots of the material unless a manufacturer or other valid scan is available.

6.5 Evaluate the product contact process material for heavy metals using Residue on Ignition followed by Emission Spectrographic or Inductively Coupled Plasma methodologies. In this case the amount of Residue on Ignition is not important except as it allows you to calculate the concentration of metals in the solid. If unacceptable levels of heavy metals are found, appropriate extracts should be tested by Atomic Absorption Spectroscopy to determine if the metals are extractable into the relevant process solution.

6.6 *Distilled Water Extract*— follow Practice F 619-79 (Reapproved 1991), Sections 6 through 12. When choosing a set of extraction conditions, choose a temperature similar to the