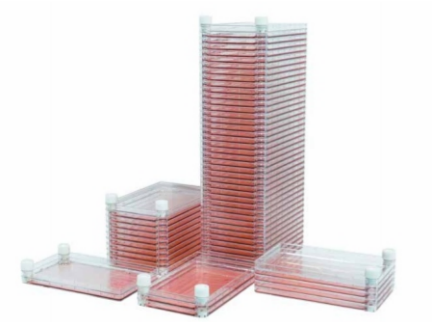

PakGent®

Cell Plant Validation Guide

No. : PG-CPVG-PT0001

Contents

How to use this guide

Scope of this publication

- This validation guide covers PakGent Cell Plant. It contains components list, test infomation, product verification information, process qualification, quality control, validation, and regulatory information.
- As of the date of this publication, data provided is current and correct.
- To verify that you have the latest version of this publication, check with your sales representative.
- Detailed test results are available for review during site audit.

Document change history

Changes are summarized and listed below

Revision	Date	Section	Description	Author
A0	01/2024	-	Initial release	Alvin Cao

Feedback on this publication

If you have any questions or concerns about the content of this publication, please contact your sales team.

Abbreviations

The list below provides definitions of abbreviations and acronyms used in this publication

ABS	Acrylonitrile Butadiene Styrene
ANSI	American National Standards Institute
ASTM	American Society for Testing and Materials
CFR	Code of Federal Regulations
COA	Certificate of Analysis
DSC	Differential Scanning Calorimetry
FDA	Food and Drug Administration
FTIR	Fourier-Transform Infrared Spectroscop
GC/MS	Gas chromatography mass spectroscopy
ICP-OES	Inductively-coupled plasma optical emission spectroscopy
IPA	Isopropyl alcohol in H_2O

ISO	International Organization for Standardization
LAL	Limulus Amebocyte Lysate
LC/MS	Liquid chromatography mass spectroscopy
NAO	Non-animal origin
NVOC	Non-volatile organic compounds
PBS	Phosphate buffered saline
RL	Reporting limit
SAL	Sterility Assurance Level
SVOC	Semi-volatile organic compounds
USP	United States Pharmacopoeia
VOC	Volatile organic compounds

Chapter 1 Introduction

The product testing and information included in this PakGent Cell Plant Validation Guide have been specifically developed to promote the use of Cell Plant in pharmaceutical and biotechnology applications.

This guide focuses on both the biological and functional performance of Cell Plant to support their use in cell culture applications. The part numbers listed below are specific to a resin or raw material. The resin or raw materal part numbers referred to within this guide are used in the manufacturing of Cell Plant systems and accessories.

Table 1.1.

Material numbers for resin and raw materials used in Cell Plant.

Description	Used in
Polystyrene resin, clear	Cell Factory trays
ABS,white	Ports and plugs
Thermoplastic vulcanizate (TPV)	Ports, plugs gasket
Tyvek foil (HDPE)	Adapter cap
Blue colorant (masterbatch)	Cover caps (blue)
HDPE,natural	Vented port closures and cover caps, blue cap, and adapter cap
PES 0.2 um air filter membrane hydrophobic	Vented port closures

Table 1.2.

Standard products for Cell Plant

Part No.	Layer	Nominal size (L x W x H)	Cell culture area	Pack
CL-MC01	1	335 x205 x 36 mm	632cm^2	6/case
CL-MC02	2	335 X205 x 53 mm	1264cm^2	6/case
CL-MC04	4	335 x205 x 87 mm	2526cm^2	6/case
CL-MC10	10	335 x205 x 189 mm	6316cm^2	6/case
CL-MC40	40	335 x205 x698 mm	25265cm^2	2/case

Chapter 2 Customer change notification process

PakGent product changes consist of modifications to a product and may include any of the following:

· Raw material changes, including resin
· Design changes that alter the dimensional specifications, functional parameters, fitness for use, or unique visual characteristics of a product
· Significant changes in manufacturing methodology that affects elements described in the following section
· Changes to the manufacturing location of product(s)
· Product deletions
· Descriptive changes affecting the company name, product name, or product item number
· Packaging changes that affect the quantity or general presentation of the product
· Mold changes
· Capacity expansion projects whereby new tooling will be added

Note:
Please note that product information contained in this validation guide is provided to the best of PakGent knowledge and belief, but without obligation or liability. This guide is not a product warranty statement or recommendation for product usage.

Any information or advice provided by PakGent herein is for reference purposes only, and does not relieve customers or users of their responsibility to determine the suitability of our products for the customer's or user's intended use. This guide is not a substitute for any part of the customer's or user's own internal validation.

Chapter 3 Design verification and validation

Our design verification and validation procedures are in compliance with ISO 13485. Meaningful design verifications and validations demonstrate compliance with release criteria and approved product claims.

Design control is an integral part of the development process to ensure the product quality and reliability.

Chapter 4 Animal origin statement

The current working definition of "animal origin" is something derived directly from animal tissue. Some of the raw materials used to produce Cell Plant systems and components may contain additives produced from bovine or porcine tallow. We confirm through supplier certifications: the source, country of origin, and BSE/TSE risk reduction steps relating to any raw materials containing tallow-derivatives.

Chapter 5 Biocompatibility

5.1

ISO 10993-1: 2018(E) - Biological evaluation of medical devices -Part 1: Evaluation and testing within a risk management process

ISO 10993-11: 2017(E) - Biological evaluation of medical devices -Part 11: Tests for systemic toxicity

ISO 10993-12: 2021(E) - Biological evaluation of medical devices -Part 12: Sample preparation and reference materials

Testing was performed on molded gamma irradiated components manufactured from the following materials:

· Polystyrene resin (cell culture product, PS)
· White acrylonitrile butadiene styrene (ABS) resin (cell culture product, ABS)
· Thermoplastic vulcanizate santoprene (cell culture product, TPV
· HDPE resin (closure HDPE)
· PES 0.2 um air filter membrane (Hydrophobic PES air filter)
· Tyvek foil (cell culture product, HDPE)
· Blue Masterbatch (cell culture product, colorant)

Summary

The material-mediated pyrogenic response test was conducted with rabbits to determine the potentia for components to produce a pyrogenic response due to intravenous exposure. All animals appeared active and healthy during the study. There were no signs of gross toxicity, adverse clinical effects, or abnormal behavior. Based on the criteria of the protocol and interpretation of the raw data according to USP-NF <151>, the test articles meets the requirements for the absence of pyrogens.

ANSI/AAMI/ISO 10993-1: 2018(E) - Biological evaluation of medical devices-Part 1: Evaluation and testing within a risk management process

10993-4: 2017: Bological evaluation of medical devices -Part 4: Selection of tests for interactions with blood

ASTM F756 - 17: “Standard Practice for Assessment of Hemolytic Properties of Materials(2017)

ASTM F619 - 20: “Standard Practice for Extraction of Medical Plastics” (2020)

materials:Testing was performed on molded gamma irradiated components manufactured from the following

Polystyrene resin (cell culture product, PS)
White acrylonitrile butadiene styrene (ABS) resin (cell culture product, ABS)
Thermoplastic vulcanizate santoprene (cell culture product, TPV)
HDPE resin (closure HDPE)
PES 0.2 um air filter membrane (Hydrophobic PES air filter)
Tyvek foil (cell culture product, HDPE)
Blue Masterbatch (cell culture product, colorant)

Summary

Testing for hemolytic potential was performed using plasma obtained from the pooled blood of healthy, experimentally naive rabbits. The analysis was used to determine whether the components has a hemolytic potential.

For the direct and indirect contact test, all test and control preparations were prepared in triplicate and analyzed using a spectrophotometer.

5.2

USP-NF- <88> Biological Reactivity Tests, In Vivo (2013) Subcutaneous Implantation Test

Testing was performed on molded gamma irradiated components manufactured from the followingmaterials:

- Polystyrene resin (cell culture product, PS)
- White acrylonitrile butadiene styrene (ABS) resin (cell culture product, ABS)
- Thermoplastic vulcanizate santoprene (cell culture product, TPV)
- HDPE resin (closure HDPE)
- PES 0.2 um air filter membrane (Hydrophobic PES air filter)
- Tyvek foil (cell culture product, HDPE)
- Blue Masterbatch (cell culture product, colorant)

Summary

A subcutaneous implantation test was conducted with Spraque-Dawley derived, albino rats to determine the potential for components to produce effects from surgical implantation, A animals survived implantation of the test article and appeared active and healthy. The difference between the mean test and control scores was 0.

Based on the criteria of the protocol and interpretation of the raw data according to USP-NF <88>, the test articles meet the requirements of the test. The test article can be classifed as USP Plastic Class VI 50°C that it was extracted at for the associated acute systemic toxicity and intracutaneous reactivity tests.

USP-NF-<88> Biological Reactivity Tests, In Vivo (2013) IntracutaneousReactivity Test

Testing was performed on molded gamma irradiated components manufactured from the followingmaterials:

- Polystyrene resin (cell culture product, PS)
- White acrylonitrile butadiene styrene (ABS) resin (cell culture product, ABS)
- Thermoplastic vulcanizate santoprene (cell culture product, TPV)
- HDPE resin (closure HDPE)
- PES 0.2 um air filter membrane (Hydrophobic PES air filter)
- Tyvek foil (cell culture product, HDPE)
- Blue Masterbatch (cell culture product, colorant)

Summary

Four extractions of the test articles in four separate vehicles and corresponding vehicle controls were each iniected intradermally (0.2 mL) on the dorsal left and right side of each animal. Each animal had the left region treated with the test article extracts. The right region of each animal was treated with physiological saline, 1 in 20 solution of ethanol in physiological saline, polyethylene glycol 400, or cottonseed oil, used as extraction controls. Dose sites were evaluated for erythema and edema immediately following all of the injections on each animal and approximately 24, 48, and 72 hours after injections.

Based on the criteria of the protocol and interpretation of the raw data according to USP-NF <88>,the test articles do meet the requirements of the test. The test article can be classified as USP Plastic Class VI-50°C.

USP-NF-<88> Biological Reactivity Tests, In Vivo (2013) Acute Systemic Toxicity Test in Mice

Testing was performed on molded gamma irradiated components manufactured from the followingmaterials:

- Polystyrene resin (cell culture product, PS)
- White acrylonitrile butadiene styrene (ABS) resin (cell culture product, ABS)
- Thermoplastic vulcanizate santoprene (cell culture product, TPV)
- HDPE resin (closure HDPE)
- PES 0.2 um air filter membrane (Hydrophobic PES air filter)
- Tyvek foil (cell culture product, HDPE)
- Blue Masterbatch (cell culture product, colorant)

Summary

An acute svstemic toxicity test in mice was conducted to determine the potential for the components to produce acute systemic toxicity from a single dose administered by a single intravenous (IV) or intraperitoneal(IP) injection.

All animals were observed for mortality, signs of gross toxicity, and behavioral changes immediately following administration. Necropsies were performed on all animals at terminal sacrifice.

Based on the criteria of the protocol and interpretation of the raw data according to USP-NF <88> the test articles do meet the requirements of the test. The test article can be classified as USP Class VI-50°C.

USP-NF-<87>. Biological Reactivity Tests, In Vitro - Elution Test In Vitro Cytotoxicity Assay:Evaluation of Test Articles

Testing was performed on molded gamma irradiated components manufactured from the followingmaterials:

- Polystyrene resin (cell culture product, PS)
- White acrylonitrile butadiene styrene (ABS) resin (cell culture product, ABS)
- Thermoplastic vulcanizate santoprene (cell culture product, TPV)
- HDPE resin (closure HDPE)
- PES 0.2 um air filter membrane (Hydrophobic PES air filter)
- Tyvek foil (cell culture product, HDPE)
- Blue Masterbatch (cell culture product, colorant)

Summary

Based on the criteria of the protocol, the test articles are not considered cytotoxic according to the Elution Test defined in USP guidelines, <87> Biological Reactivity Tests, In Vitro.

USP-NF-<85>-Bacterial Endotoxins test

Testing was performed on molded gamma irradiated components manufactured from the followingmaterials:

- Polystyrene resin (cell culture product, PS)
- White acrylonitrile butadiene styrene (ABS) resin (cell culture product, ABS)
- Thermoplastic vulcanizate santoprene (cell culture product, TPV)
- HDPE resin (closure HDPE)
- PES 0.2 um air filter membrane (Hydrophobic PES air filter)
- Tyvek foil (cell culture product, HDPE)
- Blue Masterbatch (cell culture product, colorant)

Summary
Based on the criteria of the protocol, aqueous extracts contained< 0.25 EU/ml asdetermined by the Limulus Amebocvte Lysate Test (LAL).

Chapter 6 Quality control and quality Assurance

The following Quality Control and Quality Assurance activities are performed to maintain consistent product quality and performance.

- Incoming inspection of bulk polystyrene resin
- Visual inspection of bulk polystyrene resin
- Supplier CoA

Visual inspection

In-process Cell Plant systems are inspected at regular predetermined intervals for the presence of visual defects,dimensional specifications.

Cell culture treatment verification

Cell culture treated Cell Plant systems are subjected to a steam test to verify that the cell culture treatment is uniform. Samples are taken at predetermined intervals during manufacturing.

In-line leak testing

Every Cell Plant system is leak tested in-line using a pressure-decay testing method. Pressure and measuring time parameters are pre-determined and set based on the size of the unit being tested. Pressure resistance is tested by a burst test, by increasing the pressure in the Cell Plant.

Off-line burst testing

Pressure resistance is tested by a burst test, by increasing the pressure in the Cell Plant. The test is performed at the start of each production lot and during production daily and finally after the irradiation process.

Cell culture verification testing

Cell culture testing is performed with two established for qualitative cell culture testing, and one additional cell line for quantitative cell culture testing. Testing is performed on Cell Plant representing periodically.

USP <85> Bacterial Endotoxins Test

Cell Plant is certified non-pyrogenic. Cell Plant is tested periodically using a Limulus Amoebocyte Lysate (LAL)test.

Shelf life testing/expiration dating

Accelerated and real-time aging studies have been performed and conducted according to ANSI/AAMI/ISO 11607-1:2006 and ASTM F1980-07 (2011). The results confimm that Cell Plant has a three-vear shelf life related to sterility and package integrity from the date of manufacture.

Sterility validation/verification

Bioburden determination is performed according to ISO 11737 and sterility validation is performed accordingto ISO 11137 to achieve a Sterility Assurance Level (SAL) of 10^{-6}. Dose audits are performed quarterly to re-substantiate the production dose.

BSE/TSE statement BSE/TSE

PakGent provides statements on animal-derived components for Cell Plant systems upon request.

Chapter 7 Regulatory information

7.1

General regulatory information

The intended use of the Cell Plant is large scale production of adherent cell cultures. These cultures can subsequently be used to produce secondary products, i.e. viral vaccines and therapeutic proteins. The intended use of the Assembled Tubing system mounted on the Cell Plant system is to act as a fluid pathway, facilitating controlled and aseptic addition and/or removal of liquids to the Cell Plant systems.

In conclusion and based on the product Intended Use, the Cell Plant product may be categorized as laboratory use products, with no requlatory requirements for risk-based classification nor CE-marking in EU nor according to Regulation (EU) 20171745 (MDR) or Regulation (EU) 20171746 (IVDR).

7.2

Facility certification and registration

The following table shows the certification and registration of PakGent Cell Plant manufacturing sites. Please note that PakGent does not maintain Drug Master Files for Cell Plant.