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MICROBIAL SOLUTIONS

Microbiological Quality Control Testing Solutions for Radiopharmaceutical Products

Rapid Method Applications in Nuclear Medicine

Radiopharmaceuticals used in nuclear medicine are unique medicinal formulations containing radioisotopes used in major clinical areas for diagnosis and cancer therapy. As they have decreasing content of radioactivity with time, due to radioactive decay, their physical half-lives (and correspondingly, effective shelf life) are often short – requiring final preparation shortly before administration to the patient. When administered intravenously, these products must be tested and proven sterile, according to many regulatory authorities. This includes testing for both contamination or adulteration by bacterial, fungal, or yeast microorganisms, as well as for bacterial endotoxins. However, the inherent nature of these products, which must be administered quickly upon production, poses certain challenges to the traditional test methods described in existing pharmacopeia. With the availability of simple, modern technologies and methods designed to overcome these challenges, producers of radiopharmaceutical products can provide faster, more accurate results for these tests, while ensuring patient safety.

Rapid Sterility Testing of Radiopharmaceutical Products

There is growing awareness in the regulatory landscape with regards to the limitations of the compendial sterility test of short shelf life products. In United States Pharmacopeia chapter (USP) <1071>: Rapid Microbial Tests for Release of Sterile Short-Life Products, positron emission tomographic (PET) products such as radiopharmaceuticals are listed as one of the products with recommendations that such products would benefit most from a real-time microbial test. Additionally, the European Pharmacopoeia (Ph. Eur. 2.6.1) require aseptically produced radiopharmaceuticals to be tested for sterility to eliminate the risk of contamination by microorganisms, with validated methods.

The sterility testing of PET radiopharmaceuticals also poses unique quality control problems. These drugs typically have short half-lives, often being much shorter than the incubation time required in a compendial sterility test (USP <71>; and Ph. Eur. 2.6.1 require a minimum incubation duration of 14 days of fluid thioglycollate medium and trypticase soy broth) and are administered before completion of the compendial sterility test. Secondly, aseptic operations and procedures are used to adequately ensure the sterility of the finished product – and these have more inherent risks than terminal sterilization methods. Contrary to certain opinions, PET radiopharmaceuticals have not been found to be self-sterilizing.

One such product is Fluorine-18 fluorodeoxyglucose (^{18}F-FDG), a common radiotracer used with PET imaging for diagnosis, staging, and monitoring treatment of cancers. ^{18}F-FDG has a relatively short shelf life of 109.8 minutes. This means that the product would have fully decayed by the time a 14-day traditional sterility incubation period has completed. More importantly, contaminants present may only be picked up towards the end of the 14-day period, resulting in late notifications to the facilities administering potential contaminated products to patients, as well as delayed patient interventions.

Charles River Laboratories has evaluated the feasibility of a 6-day sterility protocol using Celsis® on ^{18}F-FDG. The Celsis® 6-day Sterility protocol couples the traditional growth-based method with amplified ATP bioluminescence, thereby increasing the sensitivity and reducing the time-to-detect required to detect microbial contamination at a similar Limit of Detection (LOD) as the compendial sterility test.

In addition to being a suitable and advantageous application for rapid contamination detection, Charles River also provides validation support offering to reduce the burden on individual laboratories and manufacturers to obtain regulatory approval from local health authorities. These packages provide method equivalency validation data, as well the ability to outsource testing in the presence of your product to our laboratories or purchase the necessary test protocols to perform it in-house.

To meet the needs of radiopharmaceutical laboratories and overcome the limitations of traditional sterility testing methodologies, the following Celsis® ATP bioluminescence options are available:	
Celsis Accel® instrument	A small footprint luminometer capable of testing up to 30 assays per hour, compatible with Celsis AMPiScreen® reagents. Allows compliance with FDA 21 CFR Part 11 and European Annex 11 data integrity requirements.
Celsis Advance II™ instrument	High throughput luminometer, capable of testing 120 assays per hour, compatible with Celsis AMPiScreen®. Allows compliance with FDA 21 CFR Part 11 and European Annex 11 data integrity requirements.
Celsis AMPiScreen® reagents	Flexible 400 assay kit configuration affords convenient and efficient reagent usage, minimizing waste. Simplified reagent preparation; automated reagent injection. Compatible on both the Celsis Accel® and Celsis Advance II™ instruments.
Celsis® Complete, Sterility Service & Reports	Method validation documentation for equivalency, specificity, robustness, ruggedness, and limit of detection. CGMP validation testing in presence of product for method suitability, equivalency, limit of detection, and specificity.

Bacterial Endotoxin Testing of Radiopharmaceutical Products

Most regulatory jurisdictions now require endotoxin testing to be completed before a product is administered to a patient so that products are no longer administered at risk where pyrogenicity is concerned. Endosafe® systems utilize Limulus Amebocyte Lysate (LAL) cartridge technology to simplify and accelerate bacterial endotoxin testing. The Endosafe® LAL cartridge technology is a proven USP/EP compliant LAL testing method that provides real-time quantitative endotoxin analysis in 15 minutes using the chromogenic test methodology while eliminating the potential errors of the subjective gel-clot test method.

Licensed by the FDA in 2006 for in-process and final product release testing, the disposable pre-calibrated cartridges utilize existing FDA-licensed Endosafe® chromogenic LAL reagents (kinetic chromogenic methodology) to measure color intensity directly related to the endotoxin concentration in a sample. Each cartridge contains precise amounts of licensed LAL reagent, chromogenic substrate, and control standard endotoxin (CSE) and are manufactured according to rigid quality control procedures to ensure test accuracy and product stability. Since there is no need for positive product control or to create a standard curve or reconstitute LAL, a negative control is not needed, therefore eliminating the need for manipulating endotoxin standards, liquid reagents, and endotoxin-free accessories. By design, the Endosafe® cartridge automatically performs a duplicate sample and positive product control LAL test, thereby satisfying the harmonized USP Bacterial Endotoxin Test for LAL testing.

Compatible Radiopharmaceutical Products:

When used with any of our flexible readers, the cartridges can be used in the QC laboratory to effectively troubleshoot problematic products and to get a quick read on STAT samples and raw materials, allowing you to release PET drugs faster and reduce contaminant issues of disposables.

Endosafe® LAL cartridge technology has compatibility with a wide variety of radiopharmaceutical products including:

- [DOTA0 ,Tyr3]Octreotato (DOTATATE)
- [^{11}C]DTBZ(a)
- [^{18}F]FDG
- [^{11}C]Colina
- [^{11}C]FeCit
- [^{11}C]PK11195
- [^{11}C] Carfentanil
- Cu-ATSM
- [^{18}F]Faza
- [^{11}C]Efedrina
- [^{11}C]Flumazenil
- [^{11}C]MP4
- Y-PAGRIT
- Ga-DOTA-TOC
- LU Dotatate
- Y Zevalin
- Y Dotatoc

In addition to patient safety, laboratory technician safety should be considered when sampling and testing radioactive products. Requiring a small volume (25 μL) of product placed in secure wells, cartridge technology allows for less technician exposure and no splashing when removing and disposing of the cartridge. Endosafe instruments also allow your quality control analysts to avoid radiation exposure with the ability to view real-time test results remotely. Moreover, since radiopharmaceutical products need to reach the patient in a timely fashion, these systems also provide test results in under 15 minutes, allowing quick, confident assurance of product safety.

To meet the needs of radiopharmaceutical laboratories and sample volume, the following Endosafe testing instruments utilizing cartridge technology are available:	
Endosafe nexgen-PTS	A rapid, point-of-use, handheld spectrophotometer for precise, convenient, and real-time endotoxin testing.
Endosafe nexgen-MCS™	A multi-cartridge benchtop LAL test instrument. Addresses the need for higher sample throughput with five cartridge bays.
Endosafe Nexus™	The first fully automated robotic endotoxin testing system, which eliminates high-volume testing variables.

Holistic Quality Control of Radiopharmaceuticals

Given the increasing concern by regulatory authorities, quality assurance and quality control personnel should seek to constantly update their knowledge and implementation of faster, robust, and secure analytical methods for assessing microbiology quality control. Throughout the production process of radiopharmaceuticals, care should be given to monitor and control for contamination by sampling starting materials, radionuclide precursors, in-process controls, and finished products.

Charles River Microbial Solutions is a leading supplier for quality control solutions across a wide variety of industries, such as pharmaceutical, biologics, compounding pharmacies, cosmetics, and over-the-counter drugs. With a global network of support staff, industry experts, and constantly innovating technologies, we are committed to the safety of patients and success of the companies we partner with in building healthier lives.

Microbiological Quality Control Products

Product Name	Product Description		Product Code
Celsis Accel® instrument	Celsis® Accel.im software USB serial cable Power supply Cuvette rack Reagent drip tray		7460288
Celsis Advance II™ instrument	Celsis® Advance II.im software USB serial cable Power supply Cuvette rack Reagent rack		7456004
Celsis AMPiScreen® reagents	Celsis AMPiScreen® Pharma 100 assay kit		AS1220
Endosafe® nexgen-PTS™ instrument	Ethernet cable One-year warranty Power supply USB cable adapter Stylus		PTS150K
Endosafe® nexgen-MCS™ package	Endosafe® nexgen-MCS™ instrument EndoScan-V™ software Power supply Ethernet cable One-year warranty		MCS650K
Endosafe® LAL cartridges	10 single packs of cartridges (FDA Licensed)	Sensitivity: 0-0.1 EU/mL	PTS201F
		Sensitivity: 5-0.05 EU/mL	PTS2005F
		Sensitivity: 1-0.01 EU/mL	PTS2001F

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