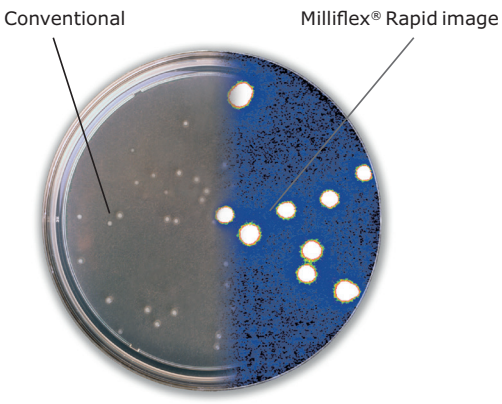
Millipore®
Preparation, Separation,
Filtration & Testing Products

Data Sheet

Milliflex® Rapid Microbiology Detection System

An automated system for rapid, accurate detection of microorganisms

The Milliflex® Rapid Microbiology Detection System is an automated solution for the rapid detection, response and resolution of microbial contamination in filterable samples throughout the manufacturing process. The system improves process control, product yield and the timely release of products. Based on Adenosine Triphosphate (ATP) Bioluminescence technology, the Milliflex® Rapid System delivers faster test results than traditional microbial contamination detection methods, such as membrane filtration (MF) and pour plates. The Milliflex® Sample Prep method also ensures consistent, reliable results. The Milliflex® Rapid System can clearly distinguish between mixed microbial growth of slow growing and fast growing microorganisms, variances in their size and ATP content in water samples.



Conventional vs. Milliflex® Rapid image analysis

Benefits

- CFU test results correlate with traditional methods
- Consistent performance delivers reproducible results
- Results in approximately one-fourth of the time of membrane filtration or pour plate methods
- Easy to operate and validate
- 21 CFR Part 11 compliance ready

Up to 4 times faster

With the Milliflex® Rapid System you can detect bacteria in approximately one-fourth the time of your current method. An intelligent system, the Milliflex® Rapid System can detect and count viable microorganisms filtered onto a membrane down to 1 CFU per sample. The software displays results as familiar colony forming units (CFU) therefore providing a direct comparison with historical data obtained from traditional methods.

Applications

Filterable samples from a wide range of industries including pharmaceutical, beverage, personal care and microelectronics:

- Raw materials
- Non-sterile final products
- In-process bioburden
- Water
- Mineral water, iced tea, flavored water, beer, wine and other beverages
- Sterility testing

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Streamlined detection and analysis

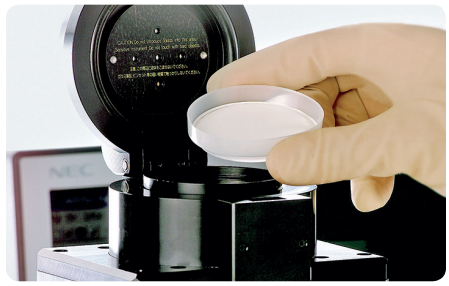
Fast, reproducible test results in three steps:

Step 1: Sample Preparation

Filter the desired sample volume through presterilized, disposable Milliflex® filter units. Filter a rinse solution to wash away any growth inhibitors (if necessary). Place filter base onto a media cassette and incubate.

Step 2: Apply Reagents

Release filter base from the Milliflex® prefilled media cassette and place filter unit on the Milliflex® AutoSpray Station for application of reagents. Reagents are automatically sprayed across the membrane in quick succession.



Step 3: Enumerate Microorganisms

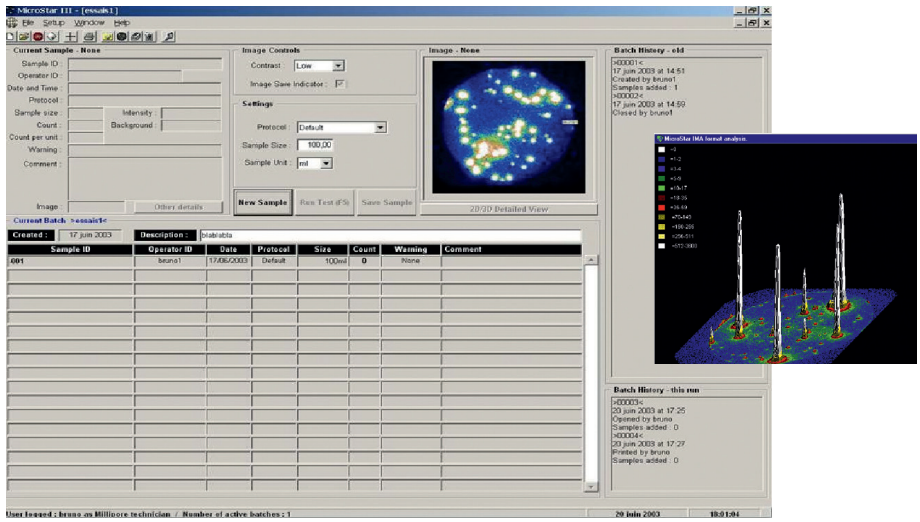
Transfer the filter unit to the Milliflex® Rapid Detection Tower for enumeration of colonies. From the PC, enter information about the sample and click the Run Test button to enumerate the microcolonies. The colony count in CFUs and an image of the filter/organisms are automatically recorded, displayed and archived.

Automated imaging analysis

The technologically advanced Milliflex® Rapid Image Analysis Software enables analysts to test water, in-process products, raw materials and final products in a fraction of the time of traditional methods. Access and editorial privileges are controlled by the system administrator ensuring secure data acquisition and retrieval.

The detection tower scans and develops an image of the microcolonies on the membrane in two minutes.

The system counts each microcolony and stores the data for downloading, printing and retrieval. Within approximately two minutes, the sample analysis and results are displayed along with the batch history and electronic image of the membrane with CFUs, which can also be viewed three dimensionally.



Current sample screen displays results of a test sample batch history. Analysts can view results as two- and three-dimensional images.

Rapid microbiology at its best

For over 15 years, Merck has set the industry standard for rapid microbiology testing. The development of the Milliflex® Rapid Microbiology Detection System is the result of years of communication and collaboration with our customers. The innovative hardware design and control software offers an easy to use, intelligent system for optimizing process control. The system includes a PC, AutoSpray Station, Detection Tower, Image Intensifier Controller and Image Analysis Software that can be used as a stand-alone test system or within a networked environment.

Merck's staff of knowledgeable and experienced microbiologists can assist with product filterability and methods development. Validation protocols, as well as on-site IQ/OQ services, service plans and training and up-to-date regulatory compliance information are also available.

Rapid sterility testing

The Milliflex® Rapid System has been proven to be used for rapid sterility testing (i.e. FDA, Center for Biologics Evaluation and Research (CBER), Rockville (MD) 2010 – Identifying faster sterility test for biological products, see additional references below).

Sterility testing is a mandatory release test for all drug products purported to be sterile in the Pharmaceutical world (EP 6.3, chapter 2.6.1, EP 7.0, chapter 5.1.9 / USP chapter 71). With the traditional sterility test an incubation time of at least 14 days is needed to get a final result. Changing the traditional test approach from liquid media incubation to solid nutrient media and the detection from visual inspection to an automated bioluminescence assay the Milliflex® Rapid Microbiology Detection System allows to reduce substantially the "time to result" down to 5 days.

Milliflex® Rapid Sterility Test has been successfully validated and implemented by different Pharmaceutical companies over the last years.

The Milliflex® Rapid Sterility Test follows the hereunder workflow:

The filtration of the samples takes place inside a sterility test isolator using three sterile 0.45 µm Milliflex® Rapid filtration devices. Incubation of the filters on the pre-filled Rapid Sterility Test Media Cassettes takes place aerobically at 20 – 25 °C, aerobically at 30 – 35 °C and anaerobically at 30 – 35 °C, to grow potential contaminants.

After 5 days of incubation, the filters are checked for visual growth. If no growth is visible, the membrane is removed from the agar and the Milliflex® Rapid reagents are sprayed onto the membrane to perform a final read out on the detection tower to check for contaminations. Subsequent identification of microorganisms is possible by re-incubation of the membrane on a new agar cassette.

The rapid sterility test with the Milliflex® Rapid System allows faster release of sterile products to the market and enables, earlier implementation of corrective actions thus avoiding loss of time and money.

Specifications

Detection Area		
Within the area of the 55 mm diameter Milliflex® membrane		
Sensitivity of System		
1 CFU/sample		
PC Configuration		
PC with Windows® 7 operating system		
Dimensions and weight		
Detection tower	Width: Depth: Height: Weight:	20 cm (8") 20 cm (8") 31 cm (12") 6 kg (13 lb)
Image intensifier controller:	Width: Depth: Height: Weight:	23 cm (9") 34 cm (13") 8 cm (3") 3 kg (7 lb)
AutoSpray Station:	Width: Depth: Height: Weight:	21 cm (8") 40 cm (16") 31 cm (12") 10 kg (22 lb)
Materials of construction – AutoSpray Station		
Turntable, pad holder, membrane holder: Cover and casing: Keypad:		316L stainless steel polyurethane polyester
Electrical		
Power supply: Consumption:		230 V, 50 Hz and 110 V, 60 Hz 30 W
Operational requirements – AutoSpray Station		
Ambient temperature: Relative humidity: Altitude:		15 – 40 °C < 90 % < 3,000 m (9,842 ft)
The AutoSpray station can be used under a laminar flow hood		
Regulatory information		
The AutoSpray Station is compliant with electro-magnetic compatibility directive 89/336/EEC and is CE marked.		

References:

1. PDA journal of pharmaceutical science and technology / PDA 65/1,42-54 1/2011: Identification of micro organisms after Milliflex® Rapid Detection – a possibility to identify non-sterile findings in the Milliflex® Rapid Sterility Test.
2. PDA journal of pharmaceutical science and technology / PDA 64/3,249-63 5/2010: Growth-promoting properties of different solid nutrient media evaluated with stressed and unstressed micro organisms: Pre-study for the validation of a rapid sterility test.
3. American pharmaceutical review, september/october 2010: Introduction of a rapid microbiological method as an alternative to the pharmacopoeial method for the sterility test.
4. Elsevier Ltd, Vaccines 29 (2011), 8012-8023: Evaluation of growth based rapid microbiological methods for sterility testing of vaccines and other biological products.

Ordering information

Description		Qty / Pk	Catalog No.
Milliflex® Rapid Microbiology Detection System Kit Includes: • Detection tower, image analyzer • CCD camera, AutoSpray station • PC with PC board and software	110	1	**MXRPKT110**
Milliflex® Rapid AutoSpray Station Includes: • AutoSpray Station, filter holder • Pad holder, 2 needle assemblies with tubing • Millex® FG vent filter, 2 stainless steel caps • Universal power supply adaptor		1	**MXRPSPRKT**
Milliflex® Plus Pump	Single Head Doube Head Triple Head	1 1 1	**MXPPLUS01** **MXPPLUS02** **MXPPLUS03**
Milliflex® Rapid Funnel, 0.45 µm membrane		24	**RMHVMFX24**
Adapter for detection tower, stainless steel, autoclavable		10	**ADAPTDT10**
Adapter for AutoSpray Station, stainless steel, autoclavable		10	**ADAPTSP10**
Milliflex® Plus Pump for usage in Isolators, Vapor Hydrogen Peroxyde (VHP) resistance and compatibility		1	**MXPPLUVHP**
Milliflex® Plus Pump Head VHP compatible		1	**MXPHEAVHP**
Positive Control Tool for fast and reliable reagent and Milliflex® Rapid System efficiency verification		1	**P0SIC0NT1**
Milliflex® Plus Pump VHP hub Kit for easy fluidic and electrical connection of Milliflex® Plus Pumps Includes: • 1 electrical hub and 3 cables, • 1 fluidic hub and 3 tubes, power supply		1	**MXPHUBKIT**
Manifold Tray for 3 Milliflex® Plus Pumps, stainless steel		1	**MXPTRAY03**
Removal rack to disconnect easily Milliflex® membrane from culture medium		1	**REMRACK01**

Description		Qty / Pk	Catalog No.
Milliflex® Rapid Kits its			
Milliflex® Rapid Reagent Kit for 100 tests • ATP releasing agent, 2 bottles • Bioluminescent reagent, 2 bottles • Reconstitution buffer, sterile, 2 bottles • 2 syringes, 5 Luer-Lok™ caps, 6 vial adapters		1	**MXRPBLRST**
Milliflex® Rapid Cleaning / Decontamination Kit For 20 cleanings, 2 decontaminations • Rinsing agent, 4 bottles • Cleaning agent, 4 bottles • Decontamination agent, 1 bottle • 10 Luer-Lok™ caps, 9 vial adapters		1	**MXRPCLKT1**
Milliflex® Rapid Cleaning / Decontamination Kit Empty bottle • 4 empty 20 mL bottles, 5 empty 10 mL bottles • 10 Luer-Lok™ caps, 9 vial adapters		1	**MXRPCLKT0**
Milliflex® Rapid Reagent Kit • 6 bottles of ATP releasing agent (5 mL per bottle) • 6 Luer-Lok™ caps, 6 vials adapters		1	**MXRPARA06**
Milliflex® Rapid Decontamination Kit • 9 bottles of decontamination vial (6.5 – 7 mL) • 10 Luer-Lok™ caps, 9 vial adapters		1	**MXRPDAG09**
Milliflex® Rapid Services			
Milliflex® Rapid Validation Protocol Includes: • IQ & OQ for AutoSpray Station and Milliflex® Rapid System	US Letter Format A4 Format	1 1	**MXRPLTVP1** **MXRPA4VP1**
Milliflex® Plus Pump Validation Protocol	Single Head Doube Head Triple head	1 1 1	**MXPP0VG01** **MXPP0VG02** **MXPP0VG03**
Milliflex® Rapid Calibration and Preventive Maintenance		1	**MXRPCLPM1**
Milliflex® Rapid Setup and Training		1	**MXRPSETUP**
Service Plans		Contact Merck	
Feasibility Study / Methods Development		Contact Merck	

21 CFR Part 11 compliance ready

Milliflex® Rapid Microbiology Detection software meets the requirements of FDA Regulation 21 CFR Part 11 for Electronic Records and Electronic Signatures. The software's powerful batch reporting feature meets the technological requirements of FDA's 21 CFR Part 11 for electronic signatures and electronic batch reporting. The batch reporting feature includes capabilities for electronic signing, performing audit trails and rendering data files unalterable.

The Milliflex® Rapid Microbiology Detection System.

Three proven technologies

The Milliflex® Rapid System uses proven technologies including membrane filtration, ATP bioluminescence and image analysis for ease of validation.

1. Membrane filtration

Today's standard for sample preparation. Large volumes of product can be processed and any inhibitor substances are easily rinsed away. Designed to optimize the enumeration of microorganisms, the Milliflex® Rapid membrane offers fast filtration and reliable results.

2. ATP bioluminescence

Found only in living cells, ATP (adenosine triphosphate) is a great indicator of cell viability. Because it is found in all microorganisms, ATP is used in a wide range of applications including raw materials, in-process product and finished products. Unlike other methods that detect both living and dead cells, the ATP method only detects viable culturable organisms, reducing false positives and improving reliability.

3. Image analysis for enumeration of microorganisms

Unlike traditional methods that require a visual inspection, the Milliflex® Rapid System uses a CCD camera to detect and enumerate microcolonies. The concentration of ATP required for measurement is about 200 attomoles, which is equivalent to one yeast or mold cell or approximately 100 bacterial cells, depending on their metabolic state. The sensitivity of the reagents combined with a charged coupled device (CCD) camera and image processor requires only a short incubation period to generate enough ATP for detection and enumeration.The system's image analysis software intensifies the bioluminescence from each cell (or microcolony) thousands of times and captures the light signals emitted from the microorganisms on the membrane with a CCD camera. An image processor enumerates the microorganisms and displays them on a computer screen.

Worldwide regulatory compliance

ATP bioluminescence technology used by the Milliflex® Rapid System is recognized as an alternative detection method by:

- FDA[1,2]
- PDA Technical Report No. 33: Evaluation, Validation and Implementation of New Microbiological Testing Methods[3]

Membrane filtration is a recommended methodology in the capture of microorganisms by worldwide pharmacopoeias (US, European and Japan). The Milliflex® Rapid System is calibrated to international light standard [LNE/NIST] and meets electrical conformity to the CE mark.

1. FDA draft guidance for industry, PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance, August 2004.
2. FDA/OPS meeting, April 13, 2004, pages 104 -110, 136.
3. PDA. May/June 2000. Technical Report No. 33: Evaluation, Validation and Implementation of New Microbiological Testing Methods. PDA Journal of Pharmaceutical Science and Technology 54(3) Supplement TR33.

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