Millipore®
Preparation, Separation,
Filtration & Monitoring Products

Data Sheet

Milliflex® Rapid System 2.0

An automated solution for rapid and accurate detection and enumeration of microorganisms

The Milliflex® Rapid System 2.0 is an automated solution for the rapid detection, imaging, and quantification of viable microbial contaminants in filterable samples throughout the manufacturing process. The system's results will help to improve process control, product yield, and the timely release of final products. In case of contamination, corrective action can be taken earlier, avoiding loss of time, money, and production capacity.

Based on highly sensitive adenosine triphosphate (ATP) bioluminescence technology, the Milliflex® Rapid System 2.0 delivers faster test results than traditional microbial contamination detection methods. Using Milliflex Oasis® sample preparation and filtration devices, the Milliflex® Rapid System 2.0 ensures consistent and reliable results. It can clearly distinguish between mixed microbial growth of slow-growing and fast-growing microorganisms, and cope with variances in colony size and ATP content.

Figure 1: Components of the Milliflex® Rapid System 2.0 setup: Milliflex Oasis® VHP resistant pump with its consumables (left), Milliflex® Rapid AutoSpray Station (center), Milliflex® Rapid Detection Tower (right)

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Benefits

The Milliflex® Rapid System 2.0 offers significant benefits for microbial contamination testing:

- Consistently fast and reproducible results
- Up to four times faster results than membrane filtration or pour plate methods
- Correlation of CFU counts with those of traditional methods
- Data integrity thanks to 21 CFR Part 11 compliant software
- Easy handling and validation

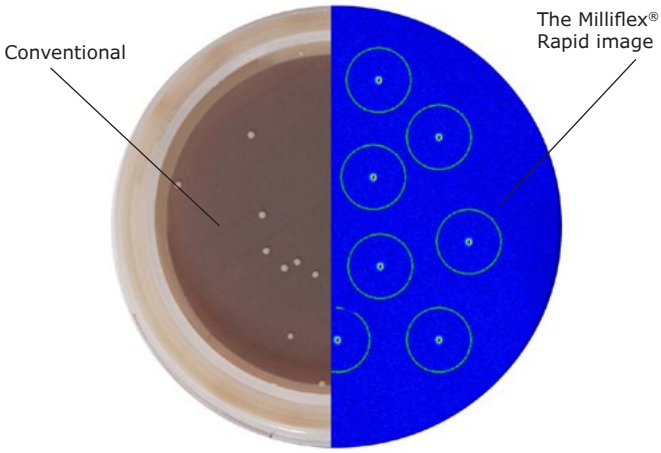

Figure 2: *C.acnes* type III on Schaeddler Blood Agar, 35°C: Conventional after 6 days (left) vs. Milliflex® Rapid after 2 days (right)

The Milliflex® Rapid System 2.0 detects microorganisms up to four times earlier than the current traditional method. Its intelligent technology recognizes and counts grown microcolonies of viable microorganisms filtered onto a Milliflex Oasis® membrane filter down to 1 colony forming unit (CFU) per sample. The software then displays the results, allowing direct comparisons with historical data obtained by traditional methods.

The Milliflex® Rapid System 2.0 can be used as a stand-alone test system or within a networked environment. It is 21 CFR Part 11 compliance ready. The system's software meets this FDA regulation's requirements for electronic records, and its powerful batch reporting feature meets the technological requirements of 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.

Applications

The Milliflex® Rapid System 2.0 is the perfect rapid solution for bioburden and sterility testing needs. It is compatible with a wide range of filterable samples from the pharmaceutical, beverage, personal care, and microelectronics industries:

- Raw materials
- Sterile and non-sterile final products
- Water samples
- Mineral water and beverages such as iced tea, flavored water, beer, and wine
- Cell-based matrices*

*Consult our application scientists for supporting protocols.

Proven technologies

The Milliflex® Rapid System 2.0 is based on three proven technologies, which makes validation easier. These are membrane filtration, ATP bioluminescence and image analysis.

1. Membrane filtration

As today's standard for sample preparation, membrane filtration allows a large volume of product to be processed, and any inhibitory substances are easily rinsed away. The method optimizes the enumeration of microorganisms by filtering fast and ensuring reliable results. Membrane filtration is the methodology that worldwide standards such as USP <61> and Ph. Eur. 2.6.12 recommend to capture microorganisms.

2. ATP bioluminescence

Found only in living cells, ATP is a great indicator of cell viability. Unlike other methods that detect both living and dead cells, the ATP method is highly reliable and consistent with the detection rates of current compendial testing methods. The ATP bioluminescence technology used by the Milliflex® Rapid System 2.0 is recognized as an alternative detection method by:

- FDA [1,2,3]
- Pharmacopeias [4]
- PDA [5]

3. Image analysis for enumeration of microcolonies

Unlike traditional methods that require visual evaluation, the Milliflex® Rapid System 2.0 uses a complementary metal oxide semiconductor (CMOS) camera to detect and enumerate any microcolonies present. The ATP concentration required for recognition is equivalent to one yeast or mold cell or approximately 100 bacterial cells, depending on their metabolic state. The camera's sensitivity, combined with state-of-the-art image analysis and optimized reagents, requires

Figure 3: Milliflex® Rapid System 2.0 Detection Tower with Milliflex Oasis® membrane filter, ready for fast reading

only a short incubation period to generate enough ATP for detection and enumeration of microcolonies. The image analysis software intensifies the bioluminescence from each microcolony a thousand times and captures the light signals emitting from the microorganisms. The software enumerates the microcolonies and displays results as familiar colony forming units (CFU).

The development of the Milliflex® Rapid System 2.0 is the result of years of communication and collaboration with our worldwide customers. Our staff of knowledgeable and experienced microbiologists can assist with product filterability challenges and method development. Validation protocols, on-site IQ/OQ services, service plans and training, and up-to-date regulatory compliance information are also available.

References:

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. Evaluation of Rapid Microbial Detection System for Testing Sterility of Biological Products Seema Parveen, Simleen Kaur, James L. Kenney, William M. McCormick, Rajesh K. Gupta Center for Biologics Evaluation and Research, FDA, Rockville, MD, Abstract # 3416
4. USP<1071> - rapid microbial tests for release of sterile short-life products: a risk-based approach.
5. 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.
6. 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.
7. 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.
8. American pharmaceutical review, september/october 2010: Introduction of a rapid microbiological method as an alternative to the pharmacopoeial method for the sterility test.
9. Elsevier Ltd, Vaccines 29 (2011), 8012-8023: Evaluation of growth based rapid microbiological methods for sterility testing of vaccines and other biological products.

General detection and analysis procedure

Step 1: Sample preparation

Filter the desired sample volume through a pre-sterilized, ready-to-use disposable Milliflex Oasis® filtration unit according to your standard operating procedure. The unit's unique Milliflex Protact® features allow for an easy and safe subsequent transfer of the membrane filter onto a Milliflex Oasis® agar plate for incubation.

Figure 4: Filterable sample being poured into a Milliflex Oasis® filtration unit

Step 2: Apply reagents

After incubation, remove the membrane filter from the Milliflex Oasis® prefilled agar plates using the membrane removal tool and place the membrane filter on the Milliflex® Rapid 2.0 AutoSpray Station to apply the reagents. Both reagents are automatically sprayed across the membrane filter in quick succession.

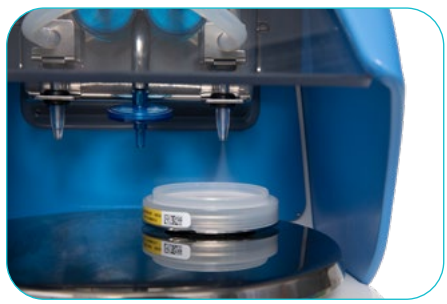

Figure 5: The AutoSpray Station applying reagent

Step 3: Enumerate microorganisms

Transfer the membrane filter to the Milliflex® Rapid System 2.0 Detection Tower for enumeration of microcolonies. Using the computer, enter sample information and run the test to count the microcolonies (reported in CFUs). An image of the membrane filter and its colonies is automatically recorded, displayed, and archived.

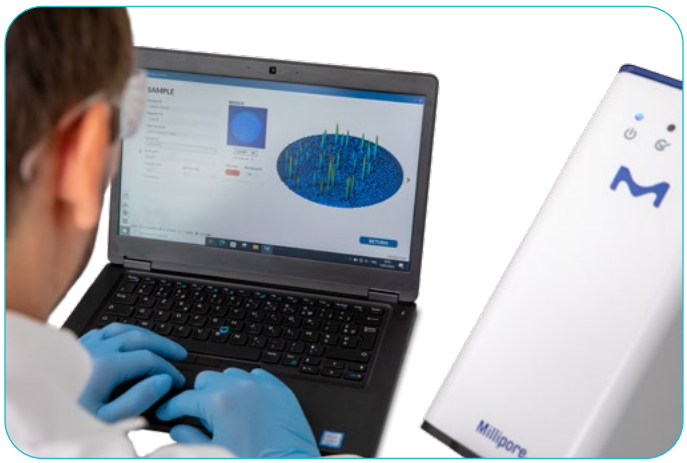

Figure 6: Computer-based result analysis with the 21 CFR Part 11 compliant Milliflex® Rapid 2.0 software.

Automated imaging analysis

The technologically advanced Milliflex® Rapid Image Analysis Software enables you to achieve results 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 system counts each microcolony and stores the data for downloading, printing, and retrieval. Within two minutes the sample is analyzed, displaying results, along with the batch history. The electronic image of the membrane and any CFUs detected is also displayed. It can be viewed in 2D or 3D.

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Frankfurter Strasse 250
64293 Darmstadt, Germany

Figure 7: Current sample screen displays the results of a test sample batch history. View results as 2D or 3D images.

Rapid sterility testing in 5 days with the Milliflex® Rapid System 2.0

Regulations and general information

The Milliflex® Rapid System 2.0 is a proven solution for rapid sterility testing which has been used by the FDA's Center for Biologics Evaluation and Research (CBER) as a faster sterility test to identify microbial contamination in biologicals (see additional references on page 3).

Sterility testing is a mandatory release test for all drug products in the pharmaceutical industry purported to be sterile (EP 6.3, chapter 2.6.1, EP 7.0, chapter 5.1.9 / USP <71>). The traditional sterility test requires an incubation time of at least 14 days to get the result. By 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 System 2.0 reduces the time-to-result substantially down to 5 days.

The Milliflex® Rapid Sterility Test has been successfully validated and implemented by various pharmaceutical companies over the years.

Overall workflow

Filtration of the samples is performed inside a sterility testing isolator using a Milliflex Oasis® VHP resistant pump and three sterile 0.45 µm pore size Milliflex Oasis® rapid filtration units. Incubation of the membrane filters on the ready-to-use media cassettes for rapid sterility testing takes place aerobically at 20 to 25 °C, 30 to 35 °C, or anaerobically at 30 to 35 °C, to grow any contaminants that may be present.

Figure 8: Milliflex Oasis® VHP resistant pump for use in a VHP isolator

After 5 days of incubation, the membrane filters are checked visually for growth. If no growth is visible, the membrane filter is removed from the agar using the Milliflex® Quantum membrane removal tool. The Milliflex® Rapid reagents are sprayed onto the membrane filter by the AutoSpray Station to then perform a final read-out on the detection tower to check for microcolonies. Subsequent identification of the microorganisms is possible by placing the membrane filter onto a new Milliflex Oasis® plate and reincubating it as traditional sterility testing requires.

Specifications

The Milliflex® Rapid System 2.0 is calibrated to international light standard [LNE/NIST] and meets electrical conformity to the CE mark.

Detection area

Within the area of the 55 mm diameter Milliflex Oasis® membrane filter

Sensitivity and LOD of system

1 CFU/sample

PC configuration

- Operating system: Windows 10 and higher version
- RAM: 8 GB
- Disk: 500 GB
- USB 3.0 port type A - female interface
- Ethernet connection

Dimensions and weight

Detection tower

Width: 30 cm (12")

Depth: 13 cm (5")

Height: 35 cm (14")

Weight: 5 kg (11 lb)

AutoSpray Station

Width: 21 cm (8")

Depth: 40 cm (16")

Height: 31 cm (12")

Weight: 10 kg (22 lb)

Materials of construction – AutoSpray Station

Turntable, pad holder, membrane holder: 316 L stainless steel

Cover and casing: polyurethane

Keypad: polyester

Electrical

Power supply: 230 V, 50 Hz, and 110 V, 60 Hz

Consumption: 30 W

Operational requirements – AutoSpray Station

Ambient temperature: 15 – 40 °C

Relative humidity: <90%

Altitude: <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 directives and is CE marked.

Ordering information

Description	Qty/Pk	Cat. No.
Kit		
Milliflex® Rapid System 2.0 - Power supply sold separately		
Kit Includes:		
•Detection tower - MXRDP2DT00	1	**MXRDP2KT01**
•AutoSpray station - MXRP2SPRKT	1	
Milliflex Oasis VHP resistant filtration pump, kit - Power supply sold separately		
Kit Includes:		
• Milliflex Oasis® VHP pump - MMPPLUVHP	2	
• Milliflex Oasis® electrical cable for connecting two Oasis VHP pumps - MMCABLEVHP	1	
• Milliflex Oasis® Pump filtration head - MMHEADMM2	4	**MMVHPKIT01**
• Sanitization kit for Milliflex Oasis® VHP resistant filtration pump - MMSANKITVHP	1	
• Stainless steel cover for Sanitization kit of Milliflex Oasis® VHP pump - MMSANKITCVR	1	
• Stainless steel plug for Milliflex Oasis® VHP pump outlet - MMVHPPLUG	2	
• Milliflex Oasis® T connectors for tubings for connecting two pumps - MMTCNNECT	1	
• Milliflex® membrane removal tool - REMRACKMM	1	
• Milliflex Oasis® vacuum gauge for pump performance testing - MMGAUGEMM	1	
Hardware		
Milliflex® Rapid System 2.0 detection tower - Power supply sold separately	1	**MXRDP2DT00**
Milliflex® Rapid System 2.0 AutoSpray station - Power supply sold separately	1	**MXRP2SPRKT**
Milliflex Oasis® filtration pump, body pump only - Power supply sold separately	1	**MMSYSTMM2**
Milliflex Oasis® VHP resistant filtration pump for use in isolator - Power supply sold separately	1	**MMPPLUVHP**

Accessories		
Milliflex Oasis® Pump filtration head	1	**MMHEADMM2**
Sanitization kit for Milliflex Oasis® filtration pump	1	**MMSANKIT1**
Sanitization kit for Milliflex Oasis® VHP resistant filtration pump	1	**MMSANKITVHP**
Stainless steel cover for Sanitization kit of Milliflex Oasis® VHP pump	1	**MMSANKITCVR**
Power supply for Milliflex Oasis® filtration pump	1	**MMPWRSP--**
Power supply for Milliflex Oasis® VHP resistant filtration pump	1	**VHPPWRSP--**
Power supply for Milliflex® Rapid System 2.0, needed for the AutoSpray Station or the detection tower	1	**MXRPWRSP--**
Milliflex® Quantum membrane removal tool	1	**REMRACKMM**
Positive Control Tool for fast and reliable Milliflex® Rapid System efficiency verification	1	**P0SIC0NT1**
Milliflex Oasis® T connectors for tubings for connecting two pumps	1	**MMTCNNECT**
Milliflex Oasis® drain tubing	1	**MMDRNTUBE**
Stainless steel plug for Milliflex Oasis® VHP pump outlet	1	**MMVHPPLUG**
Milliflex® Rapid System 2.0 door adaptor for single membrane usage (JP only)	1	**MXRP2ADAP**
Milliflex® Rapid System 2.0 USB connection cable for connecting the detection tower to PC	1	**MXRP2USBC**
Milliflex® Oasis electrical cable for connecting two Oasis VHP pumps	1	**MMCABLEVHP**
Consumables		
Milliflex® Oasis Rapid Funnel, 0.45 µm pore size PVDF membrane	24	**MMHVMFX24**
Rapid Sterility Test Medium Cassettes, double packed	20	**1460530020**
Milliflex Oasis® R2A low nutrient media plates for detection of waterborne microorganisms	48	**MMSMCRA48**
Milliflex Oasis® Tryptic Soy Media Plate for detection of aerobic and anaerobic microflora	48	**MMSMCTS48**
Milliflex Oasis® Sabouraud Dextrose Media Plate for detection of yeasts and molds	48	**MMSMCSD48**
Milliflex Oasis® flow sanitization consumable for filtration pumps	24	**MMSANSYFU**
Milliflex® Rapid Reagent Kit (100 tests)	1	**MXRPBLRST**
Milliflex® Rapid Cleaning/Decontamination Kit (20 cleanings)	1	**MXRPCLKT1**
Milliflex® Rapid Services		
Digital validation protocol on Val@M Application	1	**MXRPIQOQEP**
IQ & OQ execution service (protocol not included) combined **without** Essential PQ consultancy on Milliflex® Rapid system 2.0 at customer site	1	**MXRPVAL11**
IQ & OQ execution service (protocol not included) **combined with** Essential PQ consultancy on Milliflex® Rapid system 2.0 at customer site	1	**MXRPVAL12**
Essential PQ consultancy at customer site	1	**RSC0NSUL11**
Advanced Operator Training at customer site	1	**RSTRAIN12**

For a feasibility study, in-house or on-site evaluation, or method development service, please contact your local sales representative.

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