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PyroCell® MAT Systems

FAQs

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Logistics, Storage and Shelf Life of PyroCell® MAT Products

How do you ship the PyroCell® MAT Kits?

Depending on the scheduled transfer time, cryopreserved goods are either transported in a styrofoam box with dry ice, or in the vapor phase of liquid nitrogen (LN). Upon receiving, ensure immediate storage of components at ≤ -80°C. If dry ice is missing upon unpacking of the transport box or if vials are thawed, it is advised not to use the components as their functionality is likely impaired.

How should I store the PyroCell® MAT Kits?

Components of the PyroCell® MAT Kits must be stored at ≤ -80°C. Use of a freezer with temperature monitoring and an alarm system is recommended. Temperature excursions prior to use must be avoided in order to ensure full functionality of the pMAT cells.

Can I store the pMAT cells in liquid nitrogen?

PyroCell® MAT Kits have been validated for storage in a freezer at ≤ -80°C following transport on dry ice. Storage in liquid nitrogen after transport on dry ice is likely possible. PyroCell® MAT Kits may not be used beyond their expiry date.

Can I unpack the box with PyroCell® MAT Kits at room temperature in our lab?

Measures must be taken to avoid temperature excursion that may affect the functionality of the pMAT cells. A temperature of ≤ -80°C must be ensured. For unpacking, we recommend preparing an interim transport carrier with dry ice and fast processing to the final storage location.

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What are visible signs of temperature excursion?

Please inspect the transport box for remaining dry ice; do not use if dry ice is completely gone. Individual vials may be further inspected for even surfaces of the frozen liquid. Uneven surfaces or ice crystals inside the vial indicate temperature excursion, and components should not be used. For pMAT cells, the freeze medium should be reddish in color. A color shift from red to yellow indicates a toxicity event. Do not use pMAT cells for experiments if any of the above is observed.

What is the shelf life of the PyroCell® MAT System Kits?

pMAT cells can be used for up to 6 months after receiving. The shelf life of all other components is indicated on the vial label or the kit box label. No PyroCell® Kit components should be used beyond their expiry.

How do I store the cell culture medium before use in the MAT assay?

We recommend storing the unopened bottle of cell culture medium as stipulated by the manufacturer. An opened bottle should be stored at (2-8°C). Repeatedly warming / cooling the entire bottle with cell culture medium increases the likelihood of precipitates. Suitable aliquots ,e.g. 50 mL, may be prepared. Sterility of the cell culture medium must be ensured. Before use with MAT assays, the cell culture medium should be equilibrated to room temperature.

Preparation and Procedures for PyroCell® MAT Assays

How many test plates can I run with one of the PyroCell® MAT System Kits?

Components contained in the PyroCell® MAT System kits are sufficient to run 288 test wells or 3x 96-well microtiter plates. One vial of pMAT cells is used for one full plate. Once thawed, the pMAT cells cannot be refrozen.

How many product samples can I test with one PyroCell® MAT System Kit?

Depending on the plate layout, e.g. the number of endotoxin dilutions for the reference standard curve, the choice of controls, and the MAT method chosen (also see Ph. Eur. chapter 2.6.30), up to 3 substances can be tested per plate.

Why do I need endotoxin-free materials to conduct the MAT?

For monocyte stimulation it is mandatory to use materials that do not contain assayable levels of endotoxin in order to ensure that release of e.g. IL-6 is due to a contaminant in the test sample only. In addition, the cell culture step must be prepared aseptically using sterile materials and environment, e.g. a laminar flow hood. Once the supernatant from pMAT cell stimulation is harvested there is no further need for aseptic or endotoxin-free handling. The ELISA can be conducted on a lab bench.

What are signs of contamination during cell culture?

The primary signs of infection is turbidity of the medium and potentially color change. Cells from a contaminated culture cannot be used in the MAT assay.

What is the best practice for thawing pMAT cells prior to use in MAT?

The freeze medium for pMAT cells contains IMDM, FBS and low amounts of a cryoprotectant (DMSO). To maintain full functionality of the pMAT cells, fast thawing and immediate dilution with complete medium is mandatory. Use a water bath with a controlled temperature of 37°C and closely watch the thawing process. When you observe a remaining small ice crystal, transfer the vial contents into a 50 mL tube and immediately add the specified volume of complete medium drop-wise while swirling gently. Prolonged thawing and too fast addition of cell culture medium for dilution may impair cell viability. The dilution is sufficient, washing of the cells may lead to stress and eventually, cell loss and is not recommended.

What happens if I vortex the pMAT cells?

Do not vortex cells or solutions containing supplement. Vortexing leads to strong shear forces that may harm the cells and destroy proteins in the supplement. With certain product matrices formation of aggregates may be observed.

Would a test sample with a high or low pH impair the test results?

Yes, as it may impair the recovery of the PPC control. The IMDM medium has some buffering capacity that might be sufficient to bring a more diluted sample into the correct pH range.

What method would you recommend to determine cell viability?

Verification of cell viability upon thawing is an important parameter to ensure good assay performance. The standard manual method is Trypan Blue straining and microscopic evaluation. Alternatively, a cell counter may be used. Low cell viability can be linked to temperature excursion, improper storage or handling, i.e. prolonged thawing of the cells or fast addition of the cell culture medium.

Can I store remaining culture supernatant from the MAT stimulation?

Remaining cell culture supernatant can be stored at -20°C or -80°C for some weeks e.g. for retesting of the IL-6 cytokine. Storage time of the frozen supernatant can be dependent on the test substance used for stimulation of monocytes and needs to be empirically determined. Please note that pro-inflammatory cytokines other than IL-6 cytokines, e.g. IL-1 beta cytokines, are not stable upon freezing.

How can I remove interferences?

The most appropriate method is sample dilution. Please do not exceed the maximum valid dilution (MVD) for the test product. Extreme pH should be adjusted to a physiological pH.

Which controls should be included when running the MAT?

Complete medium is used as a negative control (blank) to verify that there are no assay-mediated pyrogens interfering with the assay (OD < 0.1). Next, each product dilution has to be tested with and without an endotoxin spike (PPC recovery at 50–200% of the spike) to verify interfering factors derived from the product. During preparatory testing, PPC recovery of two NEP controls needs to be demonstrated for the optimum dilution (50–200%). Optionally, an NEP control can be added (spiked in medium and product, recommended concentration at the EC50 of the NEP-specific standard curve). Another optional control is adding an IL-6 standard when performing the ELISA assay to verify the assay performance.

What is the best approach for finding the right sample dilution?

There are different suitable approaches. One practical approach would be:

1. Perform MAT with geometric product dilutions from the undiluted to the MVD. All dilutions are used with and without spiked endotoxin (PPC). Determine the lowest dilution /highest concentration of the sample where you find a 50–200% spike recovery.

2. In further assays, use the dilution from point 1 and geometric dilutions therefrom.

3. If there is no suitable dilution where valid spike recovery is observed, you may use Ph. Eur. chapter 2.6.30 Method 2.

When should the interference of the test product with the ELISA be determined?

There are different suitable approaches. Regulatory guidelines recommend testing the optimal product dilution found during the interference test. An alternative approach could be to exclude interference with the ELISA prior to the interference test. Here, a practical approach would be:

1. Generate a dilution series of the test product with cell culture medium e.g. 1:2, 1:10, 1:100. Make sure not to exceed the MVD.

2. With dilutions from point 1 mimic the ELISA protocol for the cell culture supernatant, e.g. 1:5 dilution with HPE buffer

3. With dilutions from point 2 perform the ELISA assay.

4. If interferences are observed test the individual product components and make a risk assessment.

What is new about the Human IL-6 Rapid ELISA?

The Pelikine Human IL-6 Rapid ELISA combines pre-coated plates with an optimized, rapid protocol. Overall, it is reducing the total ELISA assay time to 2–2.5 hours while keeping the same performance. If the same antibody conjugates, substrate and stop solution are employed, there is no need for an assay revalidation.

Assay Components and Quality Control

In which medium or buffer should I dilute my test product?

We recommend diluting the test product in IMDM (Iscove's modified Dulbecco's medium, Lonza # 12-722F). IMDM medium is also used to prepare the standard curve. It contains HEPES that neutralize inhibiting factors (e.g. pH or ionic strength). Do not use LAL water as a diluent since it causes osmotic stress.

If interferences are observed, is there a common sample treatment?

If the test sample displays extreme pH, e.g. acidic pH exceeding the buffer capacity of complete medium it is recommended to do a first dilution in PBS or TBS buffer. However, the final dilution used for cell stimulation should be in complete medium

Reference:
Molenaar-de Backer et al. (2023) "*In vitro* alternative for reactogenicity assessment of outer membrane vesicle based vaccines")

Can I use a different cell culture medium than IMDM recommended by Lonza?

Yes. However, please note that the recommended IMDM medium has been validated with the PyroCell® MAT System kits. The chosen cell culture medium should not contain assayable endotoxin levels that may interfere with the assay. If information regarding the endotoxin content is not available, we recommend testing the alternative cell culture medium with an endotoxin detection assay, e.g. kinetic chromogenic Kinetic-QCL® Kinetic Chromogenic LAL Assay, Pyrogent® 5000 Kinetic Turbidimetric LAL Assay and Pyrogene® Recombinant Factor C Assay from Lonza.

Can I use a supplement other than fetal bovine serum (FBS) when stimulating pMAT cells?

Yes. Lonza offers a choice of validated PyroCell® MAT System kits with alternative serum sources : The PyroCell® MAT System Kit uses FBS while the PyroCell® MAT HS System Kit uses human serum (HS). The choice of the serum source impacts the reactivity profile of the pMAT cells towards endotoxin and several non-endotoxin pyrogens (NEPs). The use of FBS leads to enhanced sensitivity towards bacterial endotoxin while use of HS enhances the sensitivity towards non-endotoxin pyrogens and may reduce interference effects when working with blood based products. Adding a serum source is critical. Serum-free culture medium does not support the stimulation of naive primary cells.

Reference:
Molenaar-de Backer *et al.* (2021): Performance of Monocyte Activation Test Supplemented with Human Serum Compared to Fetal Bovine Serum. ALTEX 38(2), 307-315.

How many blood donations are pooled for pMAT cells?

One production lot of pMAT cells contains equal amounts of peripheral blood mononuclear cells from four blood donations.

What is the benefit of a donor pool vs. single donors or a monocytic cell line?

Reactivity of individual donors towards NEP can be more diverse than towards endotoxins. Donor pools provide the advantage of assessing different donor profiles in one experiment compared to repeating the same experimental work with single donors. Cell lines are derived from tumor cells leading to a different reactivity profile as compared to primary cells.

What is the benefit of 8-donor pools vs. 4-donor pools?

The more donors are pooled, the larger the lot size. On the flip side, a weak reacting donor in a large pool may be overlooked. Therefore, using 4 -donor pools provides a good compromise between work load and safety.

What are the advantages of primary PBMC vs. whole blood?

A PBMC preparation enriches the white blood cells and therefore the monocytes per volume. This enhances the sensitivity of the test.

Why do I have to test against reference standard endotoxin (RSE)?

The MAT assay is a pyrogenicity test by means of secreting pro-inflammatory cytokines in response to pyrogens contained in the test substance. Enhanced IL-6 secretion is linked to the fever reaction in a patient. Endotoxin is considered the most potent pyrogen and with RSE, a calibrated standard internationally accepted that enables users to compare results between assays is available. For most substances, tolerable amounts of endotoxin are specified dependent on the route of administration. Using RSE allows the user to define a threshold dose.

Where do I find a Reference Standard Endotoxin?

Lonza catalog # E700.

Why do I need NEP (non-endotoxin pyrogen) controls?

NEP controls are required by Ph. Eur. 2.6.30 during the MAT assay qualification in a laboratory, and during product validation. Qualifying the response to NEP (that pose a risk to contaminate the product) ensures that the assay is capable of detecting a potential risk that may be contained in a substance, or derived from the production environment. NEP controls are not necessarily needed during routine testing.

Can I use any NEP preparation?

It is recommended to test NEPs that pose a risk to the specific manufacturing environment. If a commercial preparation is used, we recommend to verify that the preparation is endotoxin-free. This can be achieved with an LAL test or by using Polymyxin B to disrupt endotoxin activity.

How has Lonza selected the NEP used for quality control?

NEP used for quality control are candidates currently discussed by expert committees (e.g. WHO) to become a reference standard.

Which NEP does Lonza provide?

Lonza does not provide a NEP portfolio. For product qualification, we recommend using NEPs that are outlined in the batch-specific Certificate of Analysis.

NEP	Ligand for	Supplier	Product code
Peptidoglycan (PGN-SAndi)	NOD 1/2	InvivoGen	Tlrl-sipgn
Pam3CSK4	TLR1/2	InvivoGen	Tlrl-pms
Flagellin (FLA-ST)	TLR5	InvivoGen	Tlrl-epstfla-5
HKSA	TLR2	InvivoGen	Tlrl-hksa

What is the expected concentration range when testing NEP?

Many NEP display limitations for batch-to batch consistency and are variable between vendors. Furthermore, an influence of the product may need to be considered. Experimental data regarding performance with the PyroCell® MAT assay is indicated below, but should only be used as a rough reference.

Pyrogen	Supplier	Product Number	Estimated LOD
LPS (EU/mL)	EDQM	E0150000	≤ 0.02
LTA-SA (ng/mL)	InvivoGen	tlrl-pslta	≤ 100
Pam3CKS4 (ng/mL)	InvivoGen	tlrl-pms	≤ 0.625
FLA-BS (μg/mL)	InvivoGen	tlrl-bsfla	≤ 0.450
FLA-ST (ng/mL)	InvivoGen	tlrl-epstfla-5	≤ 0.150
HKSA (x 10e6/mL)	InvivoGen	tlrl-hksa	≤ 0.5
R848 (ng/mL)	InvivoGen	tlrl-r848-5	≤ 62.5
PGN-Sandi (μg/mL)	InvivoGen	tlrl-sipgn	≤ 2.5

How do I dilute NEP/RSE?

Commercial NEPs are very often supplied lyophilized. We recommend reconstituting and diluting NEP as stipulated by the manufacturer and performing a serial dilution in complete medium.

Which NEP should I use as control?

Optimally, a risk assessment for test product is advising the control NEPs to be considered. The table below provides examples of commonly used NEP ligands and the receptors (Toll like receptors, TLR) they respond to. According to Ph. Eur. 2.6.30, it is required to use 2 NEP for different TLR for the assay qualification.

Receptor	Pyrogen	Localization	Ligand	Origin
NOD1/2	PGN	Cytoplasm	MDP, iE-DAP	Bacteria
TLR1/TRL2	Pam3CSK4	Plasma membrane	Triacyl Lipoprotein	Bacteria
TLR2	HKSA, PGN, LTA, Zymosan	Plasma membrane	Lipoprotein	Bacteria, virus, fungi, parasite
TLR2/TLR6	FSL-1	Plasma membrane	Diacylated Lipoprotein	Bacteria, virus
TLR3	Poly-IC	Endolysosome	dsRNA	Virus
TLR4	Endotoxin	Plasma membrane	LPS	Bacteria
TLR5	Flagellin	Plasma membrane	Protein in flagella	Bacteria
TLR7 / TLR8	Imiquimod (R837) Resiquimod (R848)	Endolysosome	ssRNA	Virus, bacteria
TLR9	ODN2006	Endolysosome	CpG-DNA	Virus, bacteria, protozoa
TLR11		Plasma membrane	Profilin-like molecule	Protozoa, parasite

Examples for NEP and corresponding TLR ligands

Analysis and Interpretation of Results

What solutions is Lonza offering for analysis of the MAT assay?

For routine analysis, Lonza offers an analytics template that calculates results according to Ph.Eur. requirements.

What is the difference between 4-PLM and 5-PLM curve?

Logistic models describe sigmoidal or s-shaped dose response curves "modeled" by the single data points. A 4-parameter logistic model (4-PLM) describes a curve that is symmetric around its inflection point in the middle of the curve. The 5PLM curve describes a sigmoidal shape that is asymmetric with an inflection point above or below the middle of the curve.

What is the test sensitivity and how does it differ from the cut-off value and LOD?

The terms cut-off value and LOD depict the same information in different units. The cut-off value is expressed in optical density (OD) and the LOD is expressed in EU/mL. The cut-off value is determined by the mean value of the responses to the blank, plus three times the standard deviation. If using logistic models for statistical analysis, the cut-off value is part of the Endotoxin Standard Curve. The test sensitivity is the first dilution on the standard curve generating a response exceeding the cut-off value.

The cut-off value is calculated using the following expression:

cut off value = x + (3s)

x = mean of the four replicates of the response of the blank

s = standard deviation of the four replicates of the responses to the blank

What is the "historical LOD"?

The term "historical LOD" is a vendor defined value based on own validation data that contains a safety margin. With the release of Ph. Eur. 11.5/ 2.6.30 this term has been replaced by the term "Test Sensitivity" which represents an actual point on the standard curve closest to the cut-off value. Since the test sensitivity is influenced by experimental set-up, the calculated test sensitivity at the day of the experiment should be lower or equal to the test sensitivity claimed for the product.

How is the MVD calculated?

The MAT is used to demonstrate that the amount of pyrogens in the test product does not exceed the Contaminant Limit Concentration (CLC). Therefore, the Maximum Valid Dilution (MVD) is based on the test sensitivity of the system.

The MVD is calculated using the following expression:

MVD = (CLC x C) / Test Sensitivity

CLC = Contaminant Limit Concentration (e.g. EU/mg)

C = Concentration of test solution (e.g. mg/mL)

Test Sensitivity: the lowest endotoxin reference standard concentration on the standard curve whose response exceeds the cut-off value.

Can I dilute the test sample below the MVD?

This is not recommended.

Do I always need to use three geometric dilutions? Can the lowest dilution exceed the MVD?

Geometric dilutions (typically 2-fold) shall not exceed the MVD of the test product. It is required to always apply the same dilution factor between the three requested dilutions.

Other options to overcome this observation:

- Consider the highest dilution at the MVD and to do the geometric dilutions upwards
- Determine any dilution between a “pass” and “fail” dilution that supports three geometric dilutions
- *(optional)* change the cell culture supplement: The use of human serum may help overcome interferences derived from the product matrix
- *(optional, validation required)* use higher / lower dilution of the supernatant in the ELISA

What OD value can I expect for the highest recommended endotoxin standard dilution?

The upper asymptote of the endotoxin standard curve can be expected > 2.5 OD. The exact values may depend on the absorbance reader, the length of the monocyte stimulation period, and how the ELISA was carried out. For example, prolonged stimulation of pMAT cells or prolonged incubation with substrate may impact the OD value.

What analytical methods are described in the general Ph. Eur. chapter on MAT?

The actual revision of chapter 2.6.30 "Monocyte Activation Test" (Ph. Eur. 11.5) is describing 2 MAT methods : Method 1 is a semi-quantitative test and method 2 is a reference lot comparison test.

Lonza Analytics workbook: If a value in tab “standard curve” (for method 1) is above LOQ, it is greyed out. Is this value still considered for the calculation?

The measured value that is greyed out is included in the standard curve fitting and calculations of the fitting parameters. However, it is not included in the calculation of the sample concentrations. The value is greyed out since the absorbance increase factor, which is an adjustable variable defined in Tab “input” by the user, defines the minimal absorbance increase between 2 subsequent standards. If the OD increase is less than the absorbance increase factor defined, the higher standard won’t be considered.

Where do I get the MAT Analytics Workbook?

Please contact Lonza's Technical Support Team:

https://bioscience.lonza.com/lonza_bs/DE/en/scientific-support-team

Are there any online trainings offered?

Yes, on our QC Insider Learning platform we offer different training modules. Other online and on-site trainings are available upon request.

Regulatory Information

What is the regulatory status of the MAT?

In their Pyrogenicity Strategy from 2022, the EU commission/ EDQM announced the removal of the Rabbit Pyrogen Test from Ph. Eur. As a result, the new general chapter 5.1.13 recommends the Monocyte Activation Test if non-endotoxin pyrogens pose a contamination risk. Other world pharmacopeias, such as the United States Pharmacopeia (USP), recognized the MAT as an alternative method to the RPT. The FDA "Guidance For Industry — Pyrogen and Endotoxins testing: Questions and Answers" requires validation of the MAT according to USP <1225>. We recommend contacting your local authorities for country-specific information.

How do the methods described in the revised MAT chapter (Ph. Eur 11.5/ 2.6.30) compare to methods A, B and C?

Method A and Method B have been merged to Method 1, "semi-quantitative" test. Method C "reference lot comparison test" is now called Method 2. Analysis and acceptance criteria have been adopted.

Do I need to perform a pyrogen test in addition to an LAL test?

The required tests to ensure patient safety are described in pharmacopeial monographs for each drug substance. A pyrogen test determines all pyrogenicity while the LAL test detects and quantifies the most potent pyrogen, bacterial endotoxin. The LAL test is not capable of detecting NEP. Therefore, a pyrogen test is recommended for every new product, and the suitability of an LAL test to replace the pyrogen test may need to be determined by cross-validation.

Why do I have to perform a product-specific validation?

A product-specific validation is always required upon establishing an analytical test method, including but not limited to endotoxin and pyrogen testing. This is to ensure that the test substance will not interfere with the assay and the analyte will be reliably detected with the method chosen.

What is meant by ethical cell sourcing?

The term refers to the code of ethics issued by the International Society of Blood Transfusion (also referred to as code of conduct). Required documentation includes a signed informed consent by the donor, in this case for MAT commercialization and quality control purposes. Suppliers are further required to document full traceability of each donation while respecting the donors’ privacy.

How are the blood donors qualified?

Donors are pre-qualified and donate specifically for the MAT test purposes. Requirements for MAT donations are outlined in Ph. Eur. and include a good health status and restrictions with regards to medications for some weeks before the donation. These requirements are included in the informed consent form and are signed off by the donor on the day of donation.

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Are there MAT method validation reports available?

Yes. The MAT method has been validated for the detection of pyrogens by the European Center for the Validation of Alternative Methods (ECVAM) in 2005 and by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in 2008. Furthermore, there are several implementation reports including product-specific validation published for vaccines.

Where can I retrieve CoAs?

On the Lonza website go to **www.lonza.com/coa**. Enter the product code M2016LC (pMAT cells), M2016LS (FBS culture supplement), or M2017LS (Human Serum supplement) and the batch number that you find on the vial label. Alternatively, find the product page for each order number on the Lonza website, and find the tab CoA in the lower part of the product page.

To retrieve the CoA for the ELISA assay components, please contact our technical support team.

Are the pMAT cells controlled for infectious diseases? Is there a possibility that the blood is infectious?

Every donation used for the preparation of pMAT cells is screened (and found negative) for transfusion λ transmissible infections. This is crucial to ensuring the microbiological safety of blood products. Testing is also confirmed in the Certificate of Analysis. However, when working with human blood, protective measures should be always taken.

What is the validated time frame for the preparation of PBMC?

This measures the time from the blood donation to cryopreservation. Currently Ph. Eur. requires that the cell preparation does not take longer than 4–8 hours. Prolonged time may influence the reactivity of the cells and may lead to less reproducible results.

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