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BIO/PHARMA - MEDICAL DEVICES - COSMETICS - BIOCIDES

BioPharma Services News

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Argos Therapeutics earns global regulatory approval with Eurofins Lancaster Laboratories' rapid mycoplasma MilliPROBE® assay

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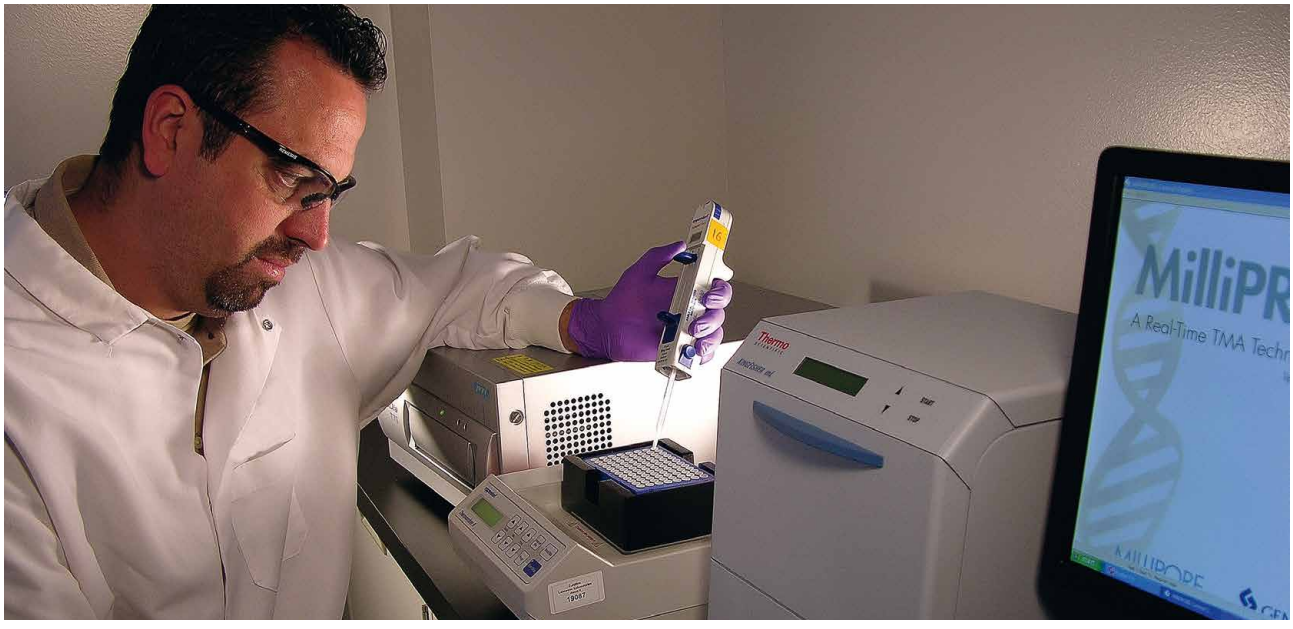
Argos Therapeutics and Eurofins Lancaster Laboratories have announced regulatory approval from authorities in the US, UK, Canada, Czech Republic and Israel for rapid mycoplasma testing of an autologous cell-based therapy produced by Argos.

Eurofins Lancaster Laboratories validated the use of the EMD Millipore MilliPROBE® system to test samples of the autologous immunotherapy currently in clinical trials for renal cell carcinoma. The assay can deliver same-day preliminary results compared to 28 days required for the standard compendial method, thereby eliminating the need to conditionally release cell-based products that require rapid turnaround time.

Mycoplasma contamination of cell lines used to produce biopharmaceutical products can disrupt cellular growth and metabolism and alter gene expression, leading to decreased product quantity and quality. World-wide regulatory agencies require that products produced in cell substrates be tested to ensure the absence of mycoplasma contamination.

The MilliPROBE® system uses Real-Time Transcription-Mediated Amplification (TMA) technology to detect targeted microbial contamination within hours compared to the weeks usually required to generate results using traditional culture-based technology. Faster detection allows biopharmaceutical manufacturers to take corrective action earlier in the production process, which reduces downstream processing risks, optimises product yields and improves final product quality. The MilliPROBE® assay probe system was designed by sequence analysis to detect Mycoplasma, Spiroplasma and Acholeplasma using a multiplex of conserved rRNA sequences in non-clinical applications. EMD Millipore has validated the non-clinical specificity and sensitivity of the system using 13 key mycoplasma species, which include the eight species specified in EP 2.6.7 . Beyond faster results, the system can process up to 20 mL of a sample, making it preferable to PCR and RT-PCR methods typically limited to testing sample volumes that are 1-2 mL.

For more information, visit *www.LancasterLabsPharm.com.*



UV-C Inactivation: A new viral inactivation method for biopharmaceuticals

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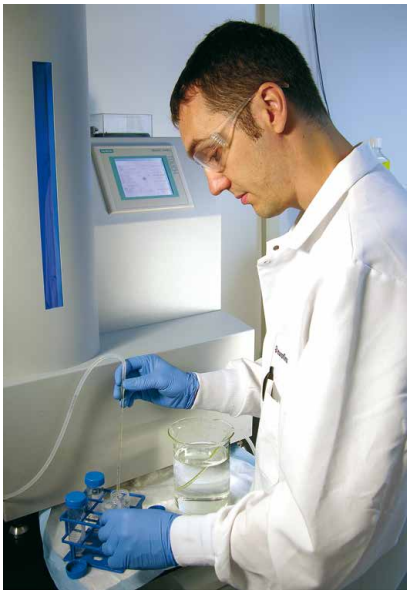
Viral clearance studies are performed for biopharmaceutical products to ensure that any virus that might be present in the starting material is removed and/or inactivated during purification. The majority of industry contamination events have historically been due to non-enveloped viruses (viruses that have no lipid envelope). Since these viruses can be difficult to inactivate, there is a need for an inactivation step that is effective on such viruses.

In collaboration with Sartorius-Stedim Biotech, Inc, Eurofins Lancaster Laboratories, Inc. scientists have been evaluating the effectiveness of UV-C treatment for inactivation of viruses. UV-C treatment at 254 nm targets primarily nucleic acids rather than proteins, so it should inactivate viruses while sparing the product.



UV-C treatment is most effective against parvoviruses such as Murine Minute Virus (MMV). This is important, as MMV is very difficult to inactivate and has been found in bioreactors a number of times over the last 20 years. Other virus families show lower inactivation that varies from family to family. The inactivation is consistent over a variety of conditions. UV-C treatment does cause product aggregation; however, typically the aggregates can be removed by subsequent purification steps.

This technology is simple to integrate into a purification process, as it operates in flow-through mode and has a very limited number of critical process parameters. We see several ways in which this new technology can be useful in assuring that viruses are not present in the final product:

- Raw materials can be treated by UV-C before they enter the bioreactor. The materials are not generally affected by UV-C, so the dose applied can be high.
- UV-C treatment can be a useful addition to a purification process for “difficult” products where it is challenging to achieve sufficient viral clearance.
- UV-C treatment can be used to replace a more complicated purification step (such as chromatography). This may allow simplification of the purification process and save costs as well as time.

For more information on how this technology can help you to achieve your viral clearance goals, visit *www.LancasterLabsPharm.com*.

Which Antimicrobial Efficacy Study is best for your product?

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The increasing number of infection rates is a severe problem in health care facilities. Medical devices coated with or including antimicrobial agents contribute to prevent infections.

To address this, BSL BIOSERVICE offers numerous test systems under ISO 17025, GLP and/or GMP to examine the antimicrobial efficacy of medical devices. The suitable test design is chosen depending on the material of the product and the aim of the study.

The following test systems serve the manufacturers to show the antimicrobial effects.

The Minimum Inhibitory Concentration (MIC) and the Minimum Bactericidal Concentration (MBC) are evaluation criteria for solutions and soluble products. A dilution series of the product is examined with a test strain by a microdilution method in 96-well plates. The lowest concentration inhibiting bacterial growth (MIC) or the reduction of the bacterial growth to 99.9 % (MBC) are determined.

For a Direct Contact Test, solid materials can be inoculated directly with a test organism. Whereas with the Dynamic Contact Test, samples of surface-bound material are shaken in the bacterial suspension. In both tests the antimicrobial effect is shown by the reduction of the microbial count within a defined time interval in comparison to a reference material.

Alternatively, solid materials are incubated on agar plates with the test strain, Agar Diffusion Test. Bacterial growth inhibition zones indicate the antimicrobial activity and are evaluated by a score system.

Regarding the Proliferation Assay, bacterial cells adhere to the material. In a second incubation step, the time-proliferation curve of daughter cells is determined by measurement of the optical density. Antimicrobial agents delay the bacterial growth.

The results of the studies help the customers for registration of their products or for marketing purposes.
For more information, visit *www.bioservice.com*.

How will the new EU 528/2013 regulation affect biocidal products testing?

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Since September 1st, 2013, the (EU) Nº 528/2013 Regulation, concerning placing on-the-market and use of biocidal products, is effectively replacing the previous 98/8/EEC Directive and introducing several novelties, some of which listed below are briefly summarised.

The Union Authorisation at ECHA (European CHemical Agengy) allows companies to apply for authorisation in several Member States simultaneously or for an EU-wide authorisation, in addition to applying for authorisation in a single Member State.

Data sharing for *in vivo* testing becomes mandatory to avoid unnecessary testing on animals. Therefore, before performing any *in vivo* tests, companies must send an inquiry to ECHA to find out whether the same test has already been conducted and submitted under EU biocides legislation. If so, companies are required to share the data.

Biocide Product Family (BPF) authorisation allows all products within a BPF to be covered by one authorisation under the Biocidal Products Regulation. A BPF is a group of biocidal products that are used for similar purposes and contain the same active substances. Any variations in the composition of the products must ensure that the level of risk is not increased and that the efficacy of the product is not reduced.

Treated article is any substance, mixture or article that has been treated with, or intentionally incorporates, one or more biocidal products and whose primary function is not as a biocide.

Eurofins has 10 years of experience in supporting companies to meet the regulatory requirements for the registration of biocidal actives and formulated products, providing a complete panel of testing for all product types. The project management is conducted by people cooperating with the European authorities and constantly updated on the news from ECHA. The Biocides Testing BU is comprised of GLP and/or ISO 17025 certified analytical, physical-chemical, efficacy and (eco)toxicological laboratories with experienced personnel dedicated to biocides testing.

For more information, visit *www.eurofins.com*.

Toxicological evaluation: the bridge between extractables and leachables

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During the drug development process, it is important to evaluate the potential for various chemicals to migrate from container closure or manufacturing systems into pharmaceutical products.

Extractables are compounds that can be extracted from the container closure system when in the presence of a solvent while leachables are compounds migrating into the drug product formulation from the container closure as a result of direct contact with the formulation.

On the basis of extractable data, toxicological evaluation gives some advice on how to design a leachable study.

The main question arising from an extractable study is about the safety of the extracted compounds.

Tolerable Intake (TI) and Threshold of Toxicological Concern (TTC) concepts can help in answering.

The TI is an estimate of the amount of a substance to which each individual may be exposed over a specified period without appreciable risk.

The TTC concept was developed to define an acceptable intake for any unstudied chemical that will not pose a risk of carcinogenicity or other toxic effects. TTC is a de facto Tolerable Intake.

In a practical sense, for a chemical with little or no toxicological data, the TTC approach is used to identify a screening intake level.

When evaluating the data coming from an extractable study, both TTC and TI can be applied.

The first step during the determination of TI is the selection of NOAEL or LOAEL coming from toxicological studies. The next step is the assessment of factors to compensate for uncertainties inherent to extrapolation of in vivo data to a given human situation. Finally, the comparison between the actual release and the TI and/or TTC is an indication about likelihood for adverse systemic effects to occur.

In the event the safety of a compound is in question, Eurofins can perform TI and TCC evaluations in real-life situations through its global leachable/extractable study capabilities. To that, Eurofins has decades of experience in helping Industries by designing and performing leachable/extractable studies and toxicological evaluations as well.

For more information visit *www.eurofins.com*.

MIND THE GAP between ISO 10993 and submission to FDA

Chiara Picotti, Eurofins BioPharma Product Testing, ChiaraPicotti@eurofins.com

ISO 10993 series regarding the biological evaluation of medical devices is considered the "gold standard" for biocompatibility issues. A new draft guidance to assist industry with ISO 10993-1 was issued by FDA in April 2013: Use of International Standard ISO 10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." This guidance is intended to replace the historical "Blue Book Memorandum #G95-1" (1995) and to address new topics regarding new materials such as nanotechnology and bioabsorbable materials.

FDA focuses also on subjects like the test selection, considering not only the nature, degree, frequency and duration of body exposure, but also the chemical characteristics of device materials (including colour additives), eventual target population and target organs. FDA encourages manufacturers to discuss their testing plans with them and affirms that safety studies performed in a relevant animal model, designed to include peculiar endpoint, may justify omission of some biocompatibility tests.

Another topic covers the samples to be tested: they should be the final products or representative coupon devices; the favourite extraction ratio is the surface/volume ratio. GLP (Good Laboratory Practices) accreditation is a must for biocompatibility reports, which should contain a well-defined test method and parameters, acceptance criteria and analysis of results. Finally, there are some new specific considerations on several tests e.g. cytotoxicity, sensitisation, pyrogenicity, implantation, genotoxicity, carcinogenicity and reproductive toxicity.

Even if this guidance hasn't been formally released, it gives clear understanding of FDA's thinking regarding biocompatibility.

Since the early '90s, Eurofins scientists have successfully performed biocompatibility testing and have the technical expertise required by the ISO 10993 and FDA guideline standard series, including *in vitro* and *in vivo* testing. During the last several decades, Eurofins has had the opportunity to participate in very interesting projects involving different kind of devices where the studies have been used for regulatory registration in many countries worldwide (CE mark in Europe, FDA submissions, Japan, Korea, China, etc.). And Eurofins' experts are currently participating in the international ISO groups in charge of the development of the ISO 10993 standards, continually staying updated on normative news and changes.

For more information on how Eurofins can help you reach FDA submission, visit *www.eurofins.com*.

COMING EVENTS

EVENT	DATE & PLACE	MORE INFO	CONTACT
Biosimilars Congregation	26-27.02.2014, London, UK	*Contact us*	*GMP_US@eurofins.com*
A3P Microbiology meeting	18-19.03.2014, Tours, France	*Contact us*	*GMP_EU@eurofins.com*
InterPhex	18-20.03.2014, New York (NY), USA	*Contact us*	*GMP_US@eurofins.com*
CASSS-Bioassays 2014	24-25.03.2014, Silver Spring (MD), USA	*Contact us*	*GMP_US@eurofins.com*
IBC Biopharmaceutical	24-27.03.2014, San Diego (CA), USA	*Contact us*	*GMP_US@eurofins.com*
PDA Annual Meeting	07-09.04.2014, San Antonio (TX), USA	*Contact us*	*GMP_US@eurofins.com*
Excipient Fest Americas	29-30.04.2014, Raleigh (NC), USA	*Contact us*	*GMP_US@eurofins.com*
E&L USA	07-09.05.2014, Silver Spring (MD), USA	*Contact us*	*GMP_US@eurofins.com*

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