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BIO/PHARMA - MEDICAL DEVICES - COSMETICS - BIOCIDES

BioPharma Services News

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Eurofins Optimed - the leading partner in Early Clinical Development

By Dr Yves Donazzolo, Eurofins Optimed, CEO & Medical Director, yvesdonazzolo@eurofins.com

Early Clinical Stages are critical in the development process to get an excellent evaluation of the safety and the efficacy of a new compound. Biotech,Medtech, big pharma and agro-food industries all need reliable partners to organise these key trials. Starting a clinical programme is always a source of anxiety for the investors and the decision makers. And expertise focused on early stages has many advantages in terms of quality, flexibility, respect of timelines and cost savings.

For 25 years, Eurofins Optimed has organised hundreds of clinical trials to support the development plans and to give accurate advice to countless R&D teams. As a leading partner, Eurofins Optimed specialises in First-Into-Human, Proof-Of-Concept, PK/PD and interactions studies.

Eurofins Optimed runs its own Clinical Pharmacology Unit in France with a dedicated team and an up-to-date equipment. Many studies involving healthy volunteers or ambulatory patients are conducted there.

Access to patients is key, and Eurofins Optimed organises the trials in many hospitals and medical centres in Europe, Western and Eastern countries.

In close collaboration with the other Eurofins sites (GMP, GLP, bioanalysis, central laboratories), Eurofins Optimed ensures a smooth process and coordination of all the stakeholders of the trials (investigators, pharmacy, monitoring, laboratories, imaging, ECG, etc.).

As data collection and data management also represent integral components of a clinical trial, Eurofins Optimed offers a global data management solutions, including database set-up, eCRF, EDC, coding or CDISC export in the Oracle Clinical® environment. Statistical analysis is then performed using SAS® in a secured and validated process.

Having earned ISO 9001:2008 certification to deliver high-standard services, the team at Eurofins Optimed is client-oriented and recognised as a leading and reliable partner for the global project management in early stages of the clinical evaluation of new compounds.

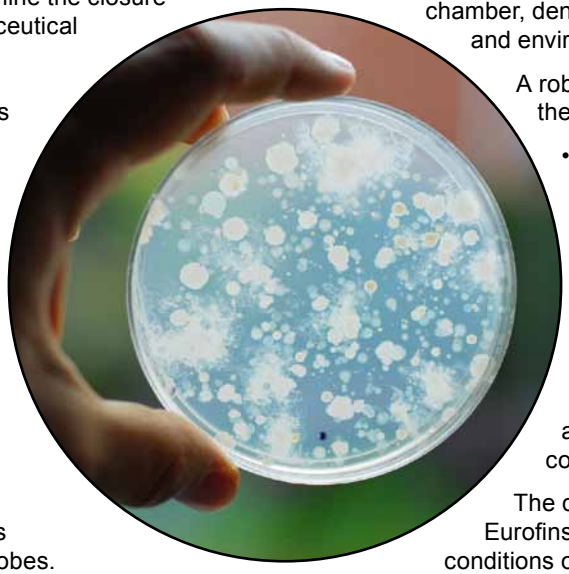
For more information, visit *www.eurofinsoptimed.com* or send an email to *optimed@eurofins.com*.

Aerosol challenge for Container Closure Integrity studies

By Michele Cavalleri, Eurofins BioPharma Product Testing Italy, MicheleCavalleri@eurofins.com

Container Closure Integrity (CCIT) studies are designed to show whether a bacterial aerosol challenge is capable of breaching the integrity of the Sponsor's sterile packaging in a worst case scenario condition.

These studies may be required to determine the closure integrity of containers for sterile pharmaceutical products or medical devices terminally sterilised in their final configuration, and when the verification of barrier properties of single components and/or bacterial immersion challenge testing are not either sufficient or relevant.



CCIT studies are performed following a sterility breach risk analysis, for instance when:

- A defect in packaging assembly might lead to aerosolised microbial contamination in class C or D environments (e.g. raised vial stoppers).
- Leaks in piping for aseptic bulk production may lead to a risk of cross contamination from aerosolised microbes.
- Sterile containers for medical devices are exposed to physical-chemical stress, which might lead to a loss of sterile barrier properties for the filters and potentially lead to cross contamination from aerosolised microbes.

The experimentation requires a robust validation of the test system. Particularly, the bacterial challenge has to be qualified in terms of challenging particle size (a high level inoculum dry spores of Bacillus atrophaeus nebulised at 60°C from a Collison NSF nebulizer), homogeneous distribution in the test chamber, density of aerosolised inoculum, flow rate, and environmental conditions.

A robust system validation requires therefore:

- The validation of reliable positivecontrols in order to verify the viability of the inoculated spores, the inoculum density and distribution, and the recovery process from the media fill.
- The validation of reliable negative controls in order to verify that the recovery process from the media fill is actually performed under aseptic conditions.

The described studies are performed by Eurofins under standard environmental conditions or at specific customised conditions of pressure, temperature, etc., in this case, a specific setup phase is strictly necessary.

For more information on conducting a CCIT study, contact: *GMP_EU@eurofins.com*.

Genotoxicity tests for medical devices: what's new in ISO 10993-3: 2014?

By Dr. Hana Hofman-Hüther, BSL BIOSERVICE GmbH (a Eurofins partner laboratory) and Paolo Pescio, Eurofins Medical Device Testing

The International Organisation for Standardisation published in October 2014 the new ISO 10993-3:2014, the most relevant standard to evaluate the potential genotoxicity, carcinogenicity, or reproductive toxicity for medical devices.

Genotoxicity tests are designed to detect substances that induce genetic damages by various mechanisms: gene mutations (point mutations) and chromosomal damage (i.e., translocations, small or large deletions and insertions, and numerical chromosomal aberrations).

A test battery is proposed because no single test method is capable of detecting all types of genotoxic effects, therefore the first *in vitro* step includes:

a) a test for gene mutations in bacteria (Ames test, OECD 471) and either

b) an *in vitro* test chromosome aberration test for chromosomal damage (OECD 473), or

c) an *in vitro* mouse lymphoma tk assay (OECD 476), or

d) an *in vitro* mammalian cell micronucleus test for chromosomal damage and aneugenicity (OECD 478).

Moreover, in the current version of the standard, the global test strategy is changed by inclusion of an *in vivo* test and a follow-up evaluation. Another relevant change is the new informative annex about guidance on selecting sample preparation procedure: inappropriate sample preparation could lead to an underestimation of genotoxicity risk, and therefore the selection of the appropriate sample preparation is crucial. Three methods are now described: beside dissolution or suspension of the test item in an adequate solvent and simulated-use extraction, a new challenging method –"Method B" encompassing extraction in two or more solvents is investigated to determine the solvent with the highest extraction residue in percent– is proposed. The selection of appropriate method depends on the chemical and physicochemical composition of the test devices.

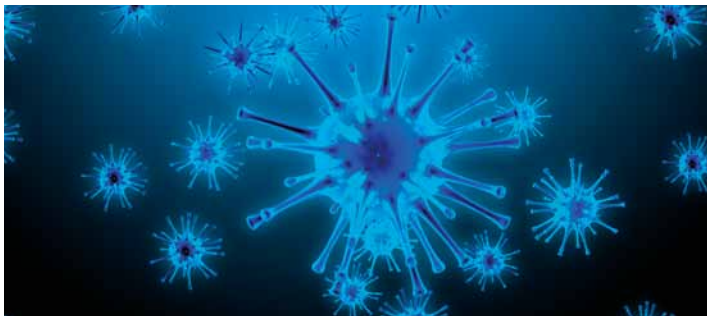
A new Supplement to ISO 10993-3:— Guidance on tests to evaluate genotoxicity [Technical Report] will describe the test requirements for medical devices and should be available in 2015.

Eurofins has decades of experience in helping industries design testing strategies as well as perform genotoxicity studies.

For the most capable genotoxicity expertise, contact: *medical-device@eurofins.com*.

EN ISO 22442 compliance for Virus Inactivation studies on Medical Devices using animal tissues and their derivatives

Alessandro Radici, Eurofins Medical Device Testing



The scope of these studies is to show in a lab scale reproducible system whether specific steps of the Sponsor's manufacturing process of a medical device incorporating biological tissue are capable of irreversibly inactivating viruses, according to EN ISO 22442 Part 3 Requirements.

As a preliminary phase, it's necessary to characterise the risk of viral contamination of the biologic material to be incorporated in the device by means of an expert assessment (literature review) of the biological material itself, the manufacturing process of both raw material and finished product as well as the potential viral inactivation steps performance.

After risk characterisation, the choice of test viruses (at least four viruses, including RNA and DNA viruses as well as enveloped and non-enveloped viruses) has to be defined; this choice is based on the following:

- Viral risk characterisation;
- Capability of viruses to grow to high titre *in vitro*;
- Detection techniques relatively easy and reproducible.

The use of model test viruses is accepted and widely used if robust official scientific literature (i.e. including relevant scientific articles, norms and regulatory guidelines) stating their equivalence in terms of taxonomy and resistance to physical-chemical stress is available.

The virus inactivation may include the validation of different types of steps, such as chemical inactivation, such as immersion in high-level disinfectant solutions, or physical inactivation, such as γ rays irradiation or moist heat treatment.

The experimental design is made typically of three phases:

1) Setup phase where virus stable titre is reached; potential residual cytotoxicity is reduced; LOQ of the method is defined and cell susceptibility to virus after exposure to treatment is assessed.
2) Inactivation kinetics are defined in terms of exposure time and/or increasing temperatures or dosage depending on the type of inactivation step.
3) Actual inactivation step in two independent replicas is simulated in lab scale, considering always a worst-case scenario (e.g. in terms of test specimen size and shape, exposure time, temperature or dosage of the treatment).

Eurofins is able to support medical device manufacturers assessing literature review and running studies under GLP certification as well.

For more information, contact: *medical-device@eurofins.com*.

Implementation of 3R-principles by Eurofins partner laboratory BSL BIOSERVICE: Determination of *in vivo* starting dose with *in vitro* methods

By Hana Hofman-Hüther, BSL BIOSERVICE GmbH (a Eurofins partner laboratory), Germany, hhofman-huether@bioservice.com

The 3Rs: Replacement, Reduction, and Refinement are important from a legal, ethical and scientific standpoint. The implementation of the 3R-principles in toxicology research by encouragement of the development and validation of effective *in vitro* alternative methods is one of the outmost concerns at BSL BIOSERVICE (a Eurofins partner laboratory).

The starting dose prediction for rodent Acute Oral Systemic Toxicity using BALB/c 3T3 NRU test is one part of this BSL BIOSERVICE strategy. The assay is designed to estimate the starting dose for *in vivo* acute oral toxicity testing by correlating the IC50 value determined in an *in vitro* cytotoxicity assay using the BALB/c 3T3 mouse fibroblast cell line with the *in vivo* LD_{50} value. However, the worldwide acceptance of the *in vitro* data is not identic. However, *in vitro* assays results were found to be significantly more predictive for acute lethality in humans (R^2 = 0.77 to 0.83) than rat and mouse LD_{50} values (R^2 = 0.65). A small step forward in the animal free age is the use of *in vitro* cytotoxicity data to determinate the starting dose for *in vivo* testing of new chemical substances as a means to reduce the numbers of animals used in LD_{50} tests. And the next step should be the use of alternative *in vitro* test battery to generate more-relevant data to evaluate human risks and reduce the time, money, and animals involved in testing.

BSL BIOSERVICE (a Eurofins partner laboratory), realising the challenges in toxicology, is pro-actively including integrated testing strategies in the safety evaluation of chemical, pharmaceutical compounds and is supporting its clients with scientific and economic knowledge and expertise in the field of alternative testing.

For more information, contact: *info@bioservice.com*.

Eurofins expands its GMP footprint in Spain

Luca Salvi, Eurofins BioPharma ProductTesting Spain, LucaSalvi@eurofins.com

In August 2014, Eurofins completed the acquisition of Sabater Pharma, a fully certified bio-pharma product testing laboratory, located in Barcelona, with an excellent reputation in the domestic market and recognised as one of the leading GMP laboratories in Spain.

This laboratory has now been merged with existing GMP operations in Barcelona and integrated into Eurofins BioPharma Product Testing global network. It counts with a surface of more than 1.700 sqm, approximately 40 FTE scientists and capabilities for fully comprehensive small molecule GMP service offerings, including: chemistry (raw materials & pharmaceutical release testing), ICH stability testing, microbiological non-sterile testing and sterility testing using isolator technology.

Fully harmonised, the laboratory adopted Eurofins BioPharma Product Testing's Quality Policy Manual, CAPA/Exceptions Management System and Document Management System. By operating under the same policies, procedures and guidelines, Barcelona's laboratory can now support the needs of multinational clients in Spain with a very high level of consistency with services provided by Eurofins in the US as well as other European countries.

This expanded GMP footprint in Barcelona allows Eurofins BioPharma Product Testing to deploy its flexible service models in Spain. In parallel with the traditional Fee for Service model, it will strongly boost *Professional Scientific Services* (PSS) for clients seeking greater flexibility in testing and staffing solutions. And, in particular, availability of space and full range of GMP testing techniques under the same roof makes this location especially suitable for our clients, *Full Time Equivalent* (FTE) programmes (dedicated full-time employees to work on client projects within our facilities).

For the most complete range of harmonised biopharmaceutical GMP product testing solutions, contact: *GMP_EU@eurofins.com*.

COMING EVENTS

EVENT	DATE & PLACE	MORE INFO	CONTACT
Pharmapack Europe	11-12.02.2015, Paris, France	*Contact us*	*GMP_EU@eurofins.com*
FARMAFOURM	04-05.03.2015, Madrid, Spain	*Booth 33*	*GMP_EU@eurofins.com*
Bio Europe	09, 10-11.03.2015, Paris, France	*Contact us*	*GMP_EU@eurofins.com*
Forum Life Science	11-12.03.2015, Munich, Germany	*Contact us*	*GMP_EU@eurofins.com*
SOT & ToxExpo	22-26.03.2015, San Diego, USA	*Booth 837*	*GMP_EU@eurofins.com*
CASSS Bioassays	23-24.03.2015,Silver Spring, MD, USA	*Contact us*	*GMP_US@eurofins.com*
Biopharm Dvlpment & Prod Week	30-31.03.2015, Huntington Beach, CA, USA	*Booth 320*	*GMP_US@eurofins.com*
ContaminExpo	31.03, 01-03.04.2015, Paris, France	*Contact us*	*GMP_EU@eurofins.com*
Interphex	21-23.04.2015, New York, NY, USA	*Booth 1410*	*GMP_US@eurofins.com*
MedTec	21-23.04.2015, Stuttgart, Germany	*Booth 7C67*	*GMP_EU@eurofins.com*
Extractables & Leachables USA	12-14.05.2015, Washington, DC, USA	*Contact us*	*GMP_US@eurofins.com*
A3P Bioproduction	26-27.05.2015, Lausanne, Switzerland	*Contact us*	*GMP_EU@eurofins.com*
Congrès SFSTP	03-04. 06.2015, La Rochelle, France	*Contact us*	*GMP_EU@eurofins.com*
Medical Device Seminar	17-18.06.2015, Munich, Germany	*Contact us*	*info@bioservice.com*

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