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BIO/PHARMA - MEDICAL DEVICES - COSMETICS - BIOCIDES

Pharma Services News

N° 04 - February 2013

New state-of-the-art Competence Centre for metals testing in pharmaceuticals and biopharmaceuticals established in Copenhagen

By Hanne Kyhnau Hansen and Jacob Jacobsen, Eurofins Pharma Product Testing, Denmark

Eurofins Pharmaceutical Products Testing has established a new state-of-the-art testing facility in Copenhagen for the testing of trace metals in pharmaceuticals, clinical and preclinical samples.

The site is equipped with ICP MS and ICP OES equipment and with Part 11 compliant software and qualified according to European and US guidelines. A special high pressure room has been established to enable detection down to ppt level, especially relevant for microscale (10 mg) analysis of tissue samples for trace metals.

Eurofins Pharma is regularly audited by FDA, European authorities and major global pharmaceutical companies and has established a strong audit track record. The Metals Team is headed by Hanne Kyhnau Hansen, with more than 15 years analytical metal testing experience, a team of senior chemists and very experienced metals analysis lab technicians. The team develops and validates analytical methods for the routine analysis of samples with critical importance for the pharmaceutical industry and routinely conducts release testing for pharmaceutical clients.

The Eurofins Pharma Products Testing Group has invested significant resources in high pressure facilities, specialised equipment for pre-treatment and analysis of samples, training of specialists, complete qualification of equipment and software in line with the Eurofins philosophy to create Centres of Excellence for highly specialised analytical purposes.

This Centre of Excellence is designed to meet the increasing demand from regulatory authorities in Europe, US and Asia for the quantification of metal impurities in pharmaceuticals in order to protect human health. The increasing quantification requirements are exemplified by the upcoming USP <232> and <233> and EP counterparts, recently introduced by US and European Pharmacopoeias.

The Metals Competence Centre in Copenhagen has been set up in close collaboration with the Metals Competence Lab located at the Eurofins Lancaster Laboratories site in the US. Both sites use the same metals testing equipment and approaches in order to facilitate a global analytical service offering for the pharmaceutical industry.

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Adventitious virus testing via Next Generation Sequencing

By Dr. Katrin Mansperger, Pharmacogenomics, Eurofins Medigenomix, Germany

Adventitious viruses are a major safety concern in biological products. For a substance to be considered free of an adventitious agent, assays must demonstrate that a defined quantity of the biological product is negative for an agent at a defined level of sensitivity. In vivo animal testing, in vitro cell culture testing, transmission electron microscopy and molecular assays like quantitative PCR (qPCR) are the current gold standards for viral safety testing. However, if for example the cell substrate contains potential contaminating agents coming from a tumor derived cell line, then current standard methods need to be supplemented by using novel technologies. Deep sequencing approaches via the Next Generation Sequencing (NGS) techniques may be the method of choice. They allow the detection not only of known viruses but also of unknown viruses or viral subspecies at the detection limit of qPCR-based methods.

Eurofins Medigenomix's adventitious virus testing experts attend the Pathogen Safety Summit 2012; they are, from left, Dr. Katrin Mansperger, Dr. Birgit Ottenwälder and Dr. Brigitte Obermaier.

At the Pathogen Safety Summit (Munich, November 27-28, 2012), the application of NGS testing approaches were introduced and intensely discussed. The application of NGS into routine testing of production cell banks is presently being evaluated by several biological and vaccine producing companies. Currently, NGS is used for initial characterisation of cell banks, but it's expected that this new technology will become a standard method for adventitious agent testing in the future. There are still challenges that need to be overcome with regard to bioinformatic analyses as well as to the speed of the technological development. Furthermore, the biological relevance of the NGS data needs to be confirmed. In this regard the expectation is that with the ability to purify active viral particles and subject them to NGS analysis, this problem can be overcome.

Eurofins Pharma Services, thanks to this new service of Eurofins Medigenomix in Ebersberg, Germany, offers the detection of adventitious viruses in biologicals and biotechnological products by Next Generation Sequencing on platforms from Illumina and Roche 454. This complements the more traditional viral detection methods being offered at Eurofins Lancaster Laboratories in the US.

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Evaluation of human skin absorption risk for pharmaceutical and cosmetic products: an in-vitro approach

By Christelle Gélis, Eurofins ADME Bioanalyses, France

It has been widely recognised that the skin can be an important route of entry for industrial chemicals and pesticides. For this reason, data on skin absorption are often required for risk assessment purposes, and both animal models and in vitro systems are used to predict skin absorption in humans.

Skin absorption studies are carried out to determine the rate at which chemicals from pharmaceutical and cosmetic products are able to penetrate skin. The chemical dermal delivery rate is mainly of interest for regulatory agencies concerned with chemical exposures in the workplace. U.S. federal and European agencies that require the submission of skin absorption data include the Environmental Protection Agency, the Food and Drug Administration, the Occupational Safety and Health Administration and the Agency for Toxic Substances and Disease Registry.

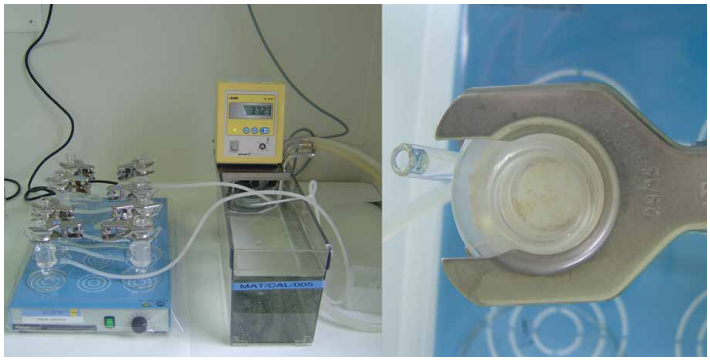

Figure 1: Franz cell in vitro model

In vitro model such as Franz cell was used with human skin coming from a surgical operation in order to evaluate the skin absorption. This approach is now accepted as a total replacement for animal-based skin absorption studies.

Absorption of a test chemical is measured over time by analysis of the receptor fluid (mimics the blood circulation) and the treated skin. The reliability and relevance of in vitro skin absorption studies have been thoroughly established through a number of international expert reviews, and these methods have been codified and accepted as an official test guideline of the Organisation for Economic Cooperation and Development (OECD).

The non-animal tests have a number of scientific advantages over the animal tests, including the ability to study a broader range of doses, including those at the actual level of exposure.

This approach allows customers to make a decision regarding the absorption of a new drug or formulation modification and evaluate the risk for human beings.

Eurofins Pharma Services designs studies that can be adapted in order to demonstrate the efficiency of a product in a specific layer of the skin and helps customer in drug candidate selection or development for topical route.

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Critical aspects of antibody-drug conjugates: structure and analysis

By Dr. Robert Duff, Eurofins Lancaster Laboratories, US

Targeted drug therapies for diseased cells (i.e. cancer) using monoclonal antibodies has been a topic of growing interest and an area of continued development. Antibody-drug conjugates (ADC) are an emerging class of targeted agents demonstrating tremendous potential both in vitro and in vivo. The mechanism of action is believed to be antigen recognition and binding followed by endocytosis during which the cell's lysosomal enzymes release the cytotoxin. These rationally designed conjugates, formed through the chemical linkage of a potent small molecule cytotoxin (drug) to a monoclonal antibody (mAb), have more complex and heterogeneous structures than the corresponding antibodies. Each part (the mAb, the drug, and the linker) must be carefully chosen in order to provide the best therapeutic index. The molecular diversity of the cytotoxins is remarkable. The commercial pipeline of antibody-based therapeutics continues to grow and now totals nearly 350 candidates.

The creation of linkers that are stable in circulation but labile upon binding of the ADC to its target has been an improvement and has resulted in the current generation of ADCs having better stability and lower systemic toxicity.

Regulatory agencies are primarily concerned with the selection of the most appropriate analytical methods for an ADC. Analytical methodologies need to discern primary structure (intact mass, peptide mapping (sequencing), NMR, FTIR, drug linkage discernment); secondary/tertiary structure (circular dichroism, SPR, X-ray), drug-antibody ratio (UV), fragments/aggregates (AUC, SEC-MALS, SE-HPLC); and charge variants (CE, iCE, IEX, MS), glycosylation and other post translational modifications (LC-MS/MS). Antigen binding, biological activities and effector function are used as appropriate (ELISA, SPR (BiaCore)). Assays for free drug and (bio)process impurities such as synthetic impurities or host cell proteins should be included.

Overall, the ADC should be considered a new molecular entity and not a combination product. ADCs show tremendous promise for the future, and now better methodologies are available to prove structure-function relationship through site-specific mAbs and non-natural amino acids.

For more information on this Eurofins Pharma service, contact: *GMP_US@eurofins.com*

Logistics and full project management: a key for success in early clinical drug development

By Dr Yves Donazzolo, Eurofins Optimed, France

Reliable and accurate conclusions of an early clinical trial are key in an effective "go/no go" decision process from First-into-Human to Proof-of-Concept in healthy subjects or patients.

Since 1990, with 100 beds dedicated to clinical pharmacology in healthy volunteers and patients and a large area for ambulatory trials, Eurofins Optimed - one of the European leaders in Early Development – has been offering a tailored, high-quality service to the pharmaceutical industry and biotechnology companies.

Indeed, Eurofins Optimed accompanies Sponsors to set up and conduct their clinical trials in many countries, identifying and coordinating all the collaborators of the clinical trial. The Project Management Team at Eurofins Optimed provides full and adapted services covering Western and Eastern Europe, including:

- Protocol development, regulatory activities (Ethics Committee and Central Authorities approvals)
- Identification & selection of investigator sites, site monitoring
- Therapeutic unit management: import, control, packaging, labelling, preparation, accountability, destruction
- Data management, eCRF solution based on Oracle Clinical secured database (accessible worldwide)
- Logistics: hospital and investigator agreements, laboratory services, human resources, sample shipment

A team with more than 20 years of experience in various therapeutic fields (Oncology, Neurology, Rheumatology, Cardiology, Dermatology) makes the difference in the organisation of an early clinical trial.

The Sponsor can request only the services needed for a great and cost-effective partnership experience.

The experience of Eurofins Optimed and its clients-driven approach, which has been awarded ISO 9001:2008 for its services, ensures Sponsors with high-level and successfully conducted clinical trials.

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Pharma Services

in brief

Quantification of residual DNA from production strains or cell lines in biopharmaceutical and biotechnological products (residual DNA testing)

By Dr. Katrin Mansperger and Dr. Sven Hoffmeyer, Pharmacogenomics, Eurofins Medigenomix, Germany

Protein based diagnostics and therapeutics gain more and more importance. These molecules are produced utilising production strains and cell lines ranging from bacteria to mammalian cell lines. Biologicals like antibodies may be contaminated with traces of nucleic acids. This residual DNA or host cell DNA is derived from the production strains (e.g. bacterial strains) or cell lines and is usually co-purified during manufacturing and purification processes. Regulatory authorities allow only very little amounts of remaining host cell DNA in biologicals. Particularly, if genetically modified organisms are used, the amount of the production strain has to be quantified during the production and purification steps as well as in the end product. Highest accuracy and sensitivity can be achieved by quantitative Real-Time PCR targeting specific DNA targets of the production strain or cell line. The development and validation of such tests are key competencies at Eurofins Medigenomix in Ebersberg, Germany. Residual DNA testing is performed in an ISO 17025 accredited laboratory and according to GxP standards. This service is also offered at Eurofins Lancaster Laboratories in the US.

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COMING EVENTS

EVENT	DATE & PLACE	MORE INFO	CONTACT
Clinical Outsourcing World Europe	6.-7.02.2013, London, UK	*Booth #001*	*clinicaltrials@eurofins.com*
Annual Biomarker Congress	19.-20.02.2013, Manchester, UK	*Booth #004*	*clinicaltrials@eurofins.com*
New Dynamics of Biomarker Labs	27.-28.02.2013, London, UK	*Booth #001*	*clinicaltrials@eurofins.com*
PDA Annual Meeting	15.-16.04.2013, Orlando, FL	*Booth #613*	*GMP_US@eurofins.com*
Partnerships in Clinical Trials	22.-24.04.2013, Orlando, FL	*Booth N°30*	*clinicaltrials@eurofins.com*
InterPhex	23.-25.04.2013, New York, NY	*Booth #1339*	*GMP_US@eurofins.com*
ECCMID	27.-30.04,2013, Berlin, Germany	*Attend only*	*clinicaltrials@eurofins.com*
BioAssay Development Conference	14.-16.05.2013, Seattle, WA	*Booth #TBD*	*GMP_US@eurofins.com*

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