New GMP unit at the Fraunhofer ITEM: certified production of investigational medicinal products will be possible as of 2008

According to European law, the production of drugs which will be used in clinical studies and have not yet been approved by the regulatory authorities is subject to exactly the same quality requirements that apply to already authorized drugs. In the sense of the German Pharmaceuticals Act, the production process, besides the actual production of medicinal products, also comprises the packaging or bottling, dilution, labeling, and release of investigational drugs. The quality standards for the production of drugs are laid down in the EU guideline for Good Manufacturing Practice (GMP).

Investigational drugs: produced individually for each patient
The Fraunhofer ITEM routinely conducts studies to test drugs intended for treatment of airway diseases. One focus of activities in this context is on therapeutic antibodies used to treat patients with bronchial asthma or chronic obstructive pulmonary disease (COPD, sometimes also referred to as "smoker’s cough"). "We receive the antibodies as a freeze-dried powder or a stem solution," explains Professor Norbert Krug, head of the Department of Clinical Airway Research. "In our studies, however, we cannot administer the antibodies in this form. From
Dear Reader,

In the future, patients suffering from respiratory diseases will increasingly be treated with more specific drugs, such as therapeutic antibodies. The amended German Pharmaceuticals Act imposes very stringent requirements on the production of drugs to be administered to humans to evaluate their effects in clinical trials in support of registration. “Production” in the sense of the Pharmaceuticals Act also includes the dilution and bottling of drugs. To be able to meet these requirements, the Fraunhofer ITEM has set up a GMP unit.

As of the beginning of next year, the Fraunhofer ITEM will additionally take over the GMP production facilities of the Helmholtz Center for Infection Research in Braunschweig. The Fraunhofer-Gesellschaft will then be the only publicly funded research organization that can produce medicinal products in compliance with GMP standards. And at the Fraunhofer ITEM in Hannover, we will thus be in a position not only to prepare novel biopharmaceuticals for clinical trials for the purpose of drug registration, but to literally produce such drugs.

In this edition, we will further present to you a new test system that allows novel biopharmaceuticals – which are tailored specifically to the human organism – to be investigated for their pharmacological efficacy and possible unwanted side effects.

Yours,
Uwe Heinrich

Prof. Dr. rer. nat. Dr. rer. biol. hum.
Director of the Institute

Editorial

this raw material, we first have to create an individualized therapeutic solution for our patients.”

In-house GMP unit is being set up

To enable compliance with the quality standards applicable to the dissolution, dilution, and bottling of investigational drugs, a certified GMP unit is currently being set up in an area of about 70 square meters. The qualification process of the clean rooms will be completed by the end of 2007.

Production facilities subject to stringent purity requirements

According to Krug, “the GMP unit is a ‘room in a room’: it consists of two production rooms.” Both rooms are shielded from the outside world by three sets of two separate airlocks, one each for staff and material, and they have to comply with the clean-room category B standard. This means that under operating conditions there must be no more than 2,000 particles larger than 5 micrometers per cubic meter of air.

These rooms of clean-room category B host the safety workbenches. Inside these workbenches, the criteria of the highest clean-room category – category A – must be met. Clean-room category A is subject to the most stringent regulations with regard to airborne particles and microbiological contamination. “In this area, measurements must remain below a single particle and a single ‘colony-forming unit’ – this is a measure of microbiological contamination – per cubic meter of air,” explains Krug.

The “four-eyes principle”

To ensure that the stringent quality requirements are met, production in the GMP unit is subject to the four-eyes principle: a qualified member of staff prepares the drug for administration, while a second person simultaneously verifies that the production rules are complied with. “Only under these stringent conditions is it allowed to dissolve and bottle sterile drugs that are to be administered intravenously to patients,” emphasizes Krug.

GMP competence to be further enhanced

In the future, the Fraunhofer ITEM will further enhance its GMP competences. At the beginning of 2008, it will take over the GMP production unit and trained staff of the Braunschweig-based Helmholtz Center for Infection Research (former GBF). This scientific competence, technology, capacity, and the required manufacturing authorization will put the Fraunhofer ITEM in a position to produce biopharmaceuticals in compliance with GMP standards. “This is an excellent complement to our GMP unit in Hannover, where subsequently to the actual production process we may then prepare the investigational drugs to be administered in clinical trials phases I and IIa,” explains Krug.

Industry standard at the research institution ITEM

GMP clean-room laboratories are standard in the pharmaceutical industry.

The Fraunhofer ITEM is now one of the few scientific institutes that are able to produce investigational drugs in an in-house GMP unit and use these in clinical studies directly on site. During the ongoing phase of performance qualification, which is to be completed by the end of 2007, it will be ensured that the GMP facilities meet the high quality standards even under workload conditions. “We have already received enquiries from companies that would like the biopharmaceuticals they have developed for treatment of airway diseases to be tested at the Fraunhofer ITEM,” says Krug.

Contact

Prof. Dr. Norbert Krug
Phone: +49 (0) 511/53 50-6 02
krug@item.fraunhofer.de
**Novel methods in testing biopharmaceuticals – Fraunhofer ITEM develops human test systems**

Today, about half of all newly developed, pharmacologically active substances are biopharmaceuticals. Most of them are proteins produced with biotechnological methods, such as growth factors, cytokines, and antibodies. “In contrast to traditional drugs, biopharmaceuticals bind very specifically to selected human cells,” explains Dr. Armin Braun, head of the Department of Immunology, Allergology and Immunotoxicology at the Fraunhofer ITEM. “This makes it difficult to subject them to a uniform registration process.” For efficacy and toxicity testing, each biotechnologically produced preparation requires a specific test system. The so far uniform strategy of testing novel substances in experimental animals is no longer practicable. Consequently, alternatives to animal experiments have to be found, for example novel in vitro test systems. To enable reliable results to be obtained, it is important that these systems be very closely related to the human organism. This is why the most appropriate test systems are, for example, cells from monkeys or even human cells.

**Sens-it-iv: an EU-wide project**

In 2006, the EU-wide project “Sens-it-iv” was initiated with a scheduled duration of five years. The aim of this project is to develop novel in vitro test systems that will allow the allergenic potential of the most different substances to be tested. Among the co-operators in this project is the Fraunhofer ITEM: “We are working to develop new in vitro test systems that will enable studies on the sensitizing potential of inhaled substances,” said Braun. To this end, scientists at the Institute use, for example, the method of precision-cut lung slices (PCLS). The lung tissue used for this comes from living animals (rodents and monkeys). Using microscopy, the interactions taking place within whole cell clusters can be monitored. In addition, PCLS make it possible to mimic physiological processes in natural cell structures and to identify the signaling substances involved.

**Human in vitro test systems**

The use of human lung tissue, however, would further improve reliability in the testing of biopharmaceuticals. The material used so far for the in vitro tests are cells obtained by lung lavage from healthy volunteers, e.g. epithelial cells or macrophages. This allows for detailed investigations into the immunological response of the cells, e.g. to biopharmaceuticals. In the future, it is intended to use also PCLS of human lung tissue, originating for example from patients with lung cancer who underwent surgery. The necessary preparations for this are under way.

**Contact:**  
Dr. Armin Braun  
Phone: +49 (0) 511/53 50-2 63  
braun@item.fraunhofer.de

**News in brief**

**Personalia**

The Quality Assurance Unit has two new staff members: Uta Dörfel, who had worked for the Department of Pathology at the Fraunhofer ITEM since 2003, has changed her field of activity as of June 15, 2007. She is replacing Dr. Lutz Peters, who retired after 28 years of work at the Institute. Like Peters, Dörfel will be concerned primarily with quality assurance tasks related to in vivo GLP studies.

Martina Heina, documentalist with a university degree, started working for the Fraunhofer ITEM in mid-August 2007. She is responsible for GCP and GMP quality assurance tasks.

“**Allergic inflammation in bronchial asthma**” was the focus of interest for the participants from the Fraunhofer ITEM at this year’s International Conference of the American Thoracic Society (ATS). A team from the Institute’s Division of Immunology, Allergology and Airway Research traveled to San Francisco between May 18 and 23, 2007 to present the latest research results of clinical and pre-clinical studies performed at the Institute. The scientists presented a total of ten posters during the Conference, dealing, among other topics, with interactions between the nervous system and allergic inflammation in bronchial asthma, or with the effects of nanoparticles on pulmonary surfactant function. Another focus was the influence of environmental factors on allergic inflammation in bronchial asthma.

For the fourth time already the Fraunhofer ITEM participated in this conference, which is the premier international forum for lung researchers.
**Bronchopulmonary Alliance**

The Department of Clinical Airway Research at the Fraunhofer ITEM cooperates with the Pulmonary Research Institute in Großhansdorf and with Parexel GmbH, the Institute of Clinical Pharmacology in Berlin. A year ago, these three institutes together founded the Bronchopulmonary Alliance, which offers studies in the area of clinical airway research to the pharmaceutical industry.

Early clinical studies to investigate chronic obstructive pulmonary diseases (COPD) are very costly and labor-intensive. Patients sometimes have to stay overnight, so that special lung function measurements can be performed. In addition, the pharmacokinetics and pharmacodynamics of the test substances have to be monitored for 24 hours.

For a single research institution, it is difficult to recruit a sufficient number of volunteers with a particular severity of disease within a short time. The fact that the Bronchopulmonary Alliance can offer identical conditions at three different locations increases its attractiveness for pharmaceutical companies.

The first joint study was undertaken in 2006, and currently the third study is going on. Up until now, the Alliance has focused its activities on testing novel substances for treating COPD in cooperation with GlaxoSmithKline. After this successful pilot phase, the scientists of all three institutes are planning to intensify their collaboration and conduct studies also for other respiratory indications as well as for other clients.

**Contact:**

Prof. Dr. Norbert Krug
Phone: +49 (0) 511/53 50-6 02
krug@item.fraunhofer.de

**New European chemicals regulation**

REACH, the new European regulation on chemicals, came into force on June 1, 2007. REACH is an acronym for "Registration, Evaluation and Authorisation of Chemicals". The new EU chemicals regulation is meant to centralize and simplify the previously valid chemicals legislation throughout the European Union.

The aim is to pool the knowledge and creativity of all players in the production chain: manufacturers and importers are required to register every chemical substance with a production or import volume of more than one tonne per year. They themselves are responsible for providing evidence, by means of appropriate data and within defined deadlines, that their substances, preparations, and products are not detrimental to health or the environment. This information is made available to further processing companies as well as to users. But at the same time, REACH requests all downstream users in the supply chain to notify manufacturers of existing and above all of any new and not yet registered applications.

The Fraunhofer ITEM has long-term experience in chemical risk assessment and offers industry a variety of services in connection with the registration process, including analysis of data gaps, comparison of substances having similar structures, the use of structure-activity relationships, and development of tailored testing strategies. Long-term contacts between the ITEM staff and both national and international regulatory authorities, active participation in their advisory committees, and cooperation with numerous scientific organizations make it easier to discuss and justify the dossiers before the regulatory authorities prior to and after submission of the registration documents.

For further information regarding our services in connection with REACH, please refer to www.item.fraunhofer.de (flyer as a PDF document, 456 KB).

**Contact:**

Dr. Gustav Könnecker
Phone: +49 (0) 511/53 50-3 28
koennecker@item.fraunhofer.de

**Cell phone radiation put to the test – results of the PERFORM-A research project published**

In 2000, the EU research project PERFORM-A was initiated, aiming to establish whether high-frequency electromagnetic fields, as they occur during the use of cellular phones, have a carcinogenic or co-carcinogenic effect in the two animal species rat and mouse. The research project was composed of four subprojects, three of which provided no evidence of the radiation emitted by cell phones being carcino-