MANUFACTURING PROCESSES FOR TISSUE ENGINEERED PRODUCTS ACCORDING TO GMP GUIDELINES
With the expertise of scientific project work and application-orientated research, we at the Fraunhofer IGB focus on the role of a mediator between preclinical research and clinical application for the development of GMP-compliant manufacturing processes for tissue engineering and Investigational Medicinal Products (IMPs). Our qualifications are based on longstanding experience in primary cell culture technologies, tissue engineering, regenerative medicine and cell therapy; assisted by an excellent network of scientists, engineers and clinicians.

Building on these skills, we develop GMP-compliant processes for the manufacture of individual, autologous tissue replacement and medicinal products for regenerative medicine and its use in clinical studies, as well as the application for Advanced Therapy Medicinal Products (ATMPs) certification of cell-based therapeutics in our certified rooms. We are well equipped to support your product pipeline.
Development of matrices and transplants

One of the focuses of our work is developing biological matrices, for example as vehicles for the manufacture of autologous transplants. We also develop acellular matrices for regenerative medicine under the Medicinal Devices Act, e.g. a collagen type I matrix made of rat’s tail tendons. We are developing implants such as stents, heart valves, and blood vessel substitutes made of synthetic and/or biological materials that can be biofunctionalized.

GMP manufacturing unit

The Fraunhofer IGB offers services in development and manufacturing of cell-based investigational medicinal products according to the EU guidelines of current “Good Manufacturing Practice” (GMP). In 2008, the GMP unit at the Fraunhofer IGB was reconstructed, completely redesigned, extended from 150 to 215 m² and reaudited by the local authorities (Regierungspräsidium Tübingen). The areas for storage and quality control now cover 100 m², classified as class D (equivalent to US class 100,000), and are completely separated from the production unit. The production facilities of class C cleanrooms (equivalent to US class 10,000) and class B (equivalent to US class 1000) add up to 110 m². The new flexibly designed areas allow an additional extension of the B area of 30 m² from the C area and v.v. The B area is divided into chambers with independent ventilation, therefore different manufacturing processes can be run simultaneously without the risk of cross-contamination. The unit is registered for genetically modified organisms up to biosafety level II (according to the German Gene Law).

New processes or proprietary manufacturing

Since 2003, the Fraunhofer IGB has been granted a Manufacturing Authorization license according to §13 German Drug Law (AMG), for autologous chondrocyte transplants. We develop and validate manufacturing processes for our partners. We produce IMPs for clinical studies in accordance to AMG or the German Medicinal Products Law (MPG). We support the subsequent clinical study and market launch.

Alternatively, we can apply for a Manufacturing Authorization for your investigational products and operate as a manufacturing site at the Fraunhofer IGB in the R&D context. In this regard, we have received several Manufacturing Authorizations in the past four years. Our customers are biotech and pharmaceutical companies as well as hospitals worldwide.

Quality assurance within all sectors

Extensive controls (bulk materials, intermediate and end products, in-process controls), complete documentation in accordance with the European guidelines, process validation and monitoring with qualified equipment and the regular training of personnel and self-inspections guarantee the quality and the safety of our products.

AMG  Arzneimittelgesetz (German Drug Law)
ATMPs  Advanced Therapy Medicinal Products
GMP  Good Manufacturing Practice
IMPs  Investigational Medicinal Products
MPG  Medizinproduktegesetz (Medical Devices Act)
PTFE  Polytetrafluoroethylene
REFERENCES

Current Projects

**Cell-free collagen implant is a medical device for the articular cartilage**
Cartilage damage is the most common form of joint disease. Recently, the German biotechnology company Amedrix has developed collagen implants for damaged cartilage that allow cells from surrounding tissues to migrate into the implants. The processes for collagen purification as well as GMP-compliant manufacturing of the collagen implants were developed in cooperation with the Fraunhofer IGB.

**Portable, individualized lung replacement**
In cooperation with the German company NovaLung, the Fraunhofer IGB is developing a method to cellularize a lung replacement system with a patient’s own cells. This is intended to minimize biocompatibility problems, which will result in extending the use of the system. The miniaturized lung replacement system and cells are to be developed at the Fraunhofer IGB under GMP conditions by AMG for clinical trials. The work is part of a project funded by the European Union’s Seventh Framework Programme for research, technological development and demonstration.

Completed Projects

**Cartilage transplant**
Autologous cartilage cells were arthroscopically removed and then expanded and embedded in a collagen matrix. The implant was designed to be easily modified to fit the cartilage defect’s size, depth and shape.

**Skin graft for poorly healing wounds**
Cells were isolated from the roots of patient’s skin hair and differentiated in culture into multilayer epithelial sheets that were used to treat poorly healing wounds.

**Melanocyte graft for therapy of vitiligo**
Vitiligo is a chronic disorder involving the partial depigmentation of the skin, which has not been considered curable to date. A new therapeutic approach for the treatment of vitiligo is now available in the form of an autologous melanocyte graft developed at the Fraunhofer IGB. The graft involves a melanocytes cell implant to reseed the diseased, pigment-free skin areas, promoting the re-pigmentation of the skin and activating melanocyte growth.
**Mesenchymal stem cells**
Mesenchymal stem cells (MSCs) are known to have regeneration benefits and are of particular interest in the fields of bone and cardiac repair. A method for producing an MSC cellular graft under GMP guidelines was developed at the Fraunhofer IGB.

**Regeneration of bone with Tissue Repair Cells**
Tissue Repair Cells are Aastrom’s bone marrow-derived autologous stem and progenitor cells. After ex vivo culture, they are used for repairing bone fractures. The efficacy of these cells in the regeneration of vessels and the heart are being investigated in clinical trials. In contract for Aastrom, the Fraunhofer IGB has manufactured the cells for the trials in Europe.

**Vascular grafts for bypass operations**
Vascular prostheses coated with autologous endothelial cells were developed for use in cardiovascular bypass surgeries. The autologous endothelial cells minimize this risk of thrombosis and were produced by AMG guidelines at the Fraunhofer IGB.
SERVICES AT A GLANCE

- Process development of autologous transplants
- Manufacturing of cell- and matrix-based transplants for phase I/II clinical studies
- Production and quality control of cell-based investigational medicinal products (IMPs) for phase I/II clinical studies
- Regulatory and documentation management
- Quality assurance

**GMP at Fraunhofer IGB**
- 215 m² flexible GMP unit
- Production facilities of class A inside B cleanrooms
- Production facilities with class C cleanroom
- Separate units for quality control and storage (class D)
- Validated processes with qualified equipment
- Quality assurance system covering production, quality control and process development
- Laboratory tract of 500 m² for research and development

**Quality assurance**
- Qualified, trained personnel
- Facilities and equipment of defined quality status
- Documentation system based on specifications and standard operation procedures for manufacturing and packaging
- Production: in-process controls, prevention of cross-contamination
- Quality control of raw materials, packaging materials, intermediate, bulk and end products
- Certified suppliers
- Self-inspection

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Fraunhofer IGB
The Fraunhofer IGB develops and optimizes processes and products in the fields of medicine, pharmacy, chemistry, the environment and energy. We combine the highest scientific standards with professional know-how in our competence areas of Interfacial Engineering and Materials Science, Molecular Biotechnology, Physical Process Technology, Environmental Biotechnology and Bioprocess Engineering, as well as Cell and Tissue Engineering – always with a view to economic efficiency and sustainability. Our strengths are to offer complete solutions from laboratory scale to pilot plant. Customers also benefit from the constructive interplay of the various disciplines at our institute, which opens up new approaches in areas such as medical engineering, nanotechnology, industrial biotechnology, and environmental technology. The Fraunhofer IGB is one of 67 institutes and independent research units of the Fraunhofer-Gesellschaft, Europe’s largest organization for application-oriented research.

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