Fraunhofer
IME

FRAUNHOFER INSTITUTE FOR MOLECULAR BIOLOGY AND APPLIED ECOLOGY IME

INTEGRATED PRODUCTION PLATFORMS

GMP-COMPLIANT PRODUCTION OF BIOPHARMACEUTICALS

Close-up of large scale UF/DF control unit

conditions and the automated transient transfection of plants, as well as rooms for the pilot-scale preparation of plant extracts, will be completed by mid-2017.

Production equipment, GMP facility

- Automated raw material weighing, recipe management and raw material lot tracking system
- Single-use buffer and media compounding system and liquid handling
- 15, 100 and 350 L bioreactors (working volume) with mechanical foam breakers allowing high-cell-density microbial processes without antifoam
- Online methanol control for methylotrophic yeast cultivation
- Solids-discharging centrifuge and disc stack separator
- French-press type homogenizers
- Tangential flow filtration devices for the 100 mL to 1000 L scale
- Pilot and process scale chromatography controllers
- RO, WFI and clean steam generation, WFI hot loop
- Capacity to handle S2 organisms

800 L extraction and filtration plant in monitored enviroment

GMP MINDSET

The development of powerful tools in life sciences research and the enormous increase in screening capacity for novel therapeutics have fueled a dramatic rise in the number of biopharmaceutical candidates in the development pipelines of global players and SMEs. Active pharmaceutical ingredients (APIs) must be produced according to good manufacturing practice (GMP) for clinical trials. As soon as proof-of-principle for a drug candidate has been established and a molecule is needed in milligram to gram quantities for characterization and preclinical testing, production process development begins to ensure the API is produced with sufficient quality at an acceptable scale and cost while complying with regulatory requirements. Profound knowledge of such requirements at the earliest stages is necessary to avoid flaws and dead-ends in process development, and to compile the necessary documentation ahead of clinical testing. Ideally, the institution that carries out process development should be linked to a GMP facility that can manufacture the clinical-grade API. For academic groups or SMEs wishing to move a drug candidate from proof-of-principle towards clinical trials, many organizational, regulatory and technical questions are likely to arise before manufacturing can begin, and the more

Diafiltration during downstream-processing of a drug substance

competence a CRO/CMO offers to its customers, the easier it is to address these questions in time

Process development

Fraunhofer IME operates an API production and purification facility that serves internal and external customers requiring the production and purification of recombinant proteins in the gram range from bacteria, yeast, plant and animal cell cultures, as well as intact plants. Process development is carried out and non-GMP material is produced in nine bioreactors ranging from 1 to 100 L working volume. All reactors support high-cell-density microbial processes requiring high oxygen transfer rates as well as animal or plant cell cultures. Animal cell culture processes can be scaled up to 100 L working volume in shaken single-use bioreactors (SUBs) and perfusion processes can be scaled up to 10 L working volume. Matching downstream processing equipment is available (separation, filtration and chromatography) as well as diverse range of sophisticated protein analytics.

Multi-purpose GMP facility

A multi-purpose GMP-compliant pilot production plant for bio-pharmaceutical APIs is available at the Fraunhofer IME in Aachen.

Lyophilized API in glas vials

The facility houses two independent multi-purpose protein production lines (fermentation volumes of 15, 100 and 350 L for microbial processes and 2 x 50 L stirred-tank SUBs with a buffer capacity of up to 2000 L per week for animal cell culture) with completely separate rooms and HVAC systems in cleanroom classes D (Fermentation and Recovery) and C (Downstream Processing). Class D in-process control, media preparation, cleaning and storage rooms complete the suite that was built according to the state of the art in cleanroom technology.
Our customers include scientists from universities and research institutes as well as SMEs who wish to move their products towards commercialization while maintaining independence, as well as global players with the need to reduce the time-to-market and outsource development. In March 2009, Fraunhofer IME was granted a manufacturing license for the production of biopharmaceutical APIs in microbial systems for clinical trials. In November 2009, the license was extended to include bulk API manufactured using transgenic plants. Six customer audits have been completed successfully and clinical-grade APIs have been produced using tobacco, *Escherichia coli* and *Pichia pastoris* as host systems in GMP campaigns. We are currently pursuing an extension of the manufacturing authorization include animal cell culture systems. A dedicated facility for the automated growth of transgenic or wild-type plants under controlled

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