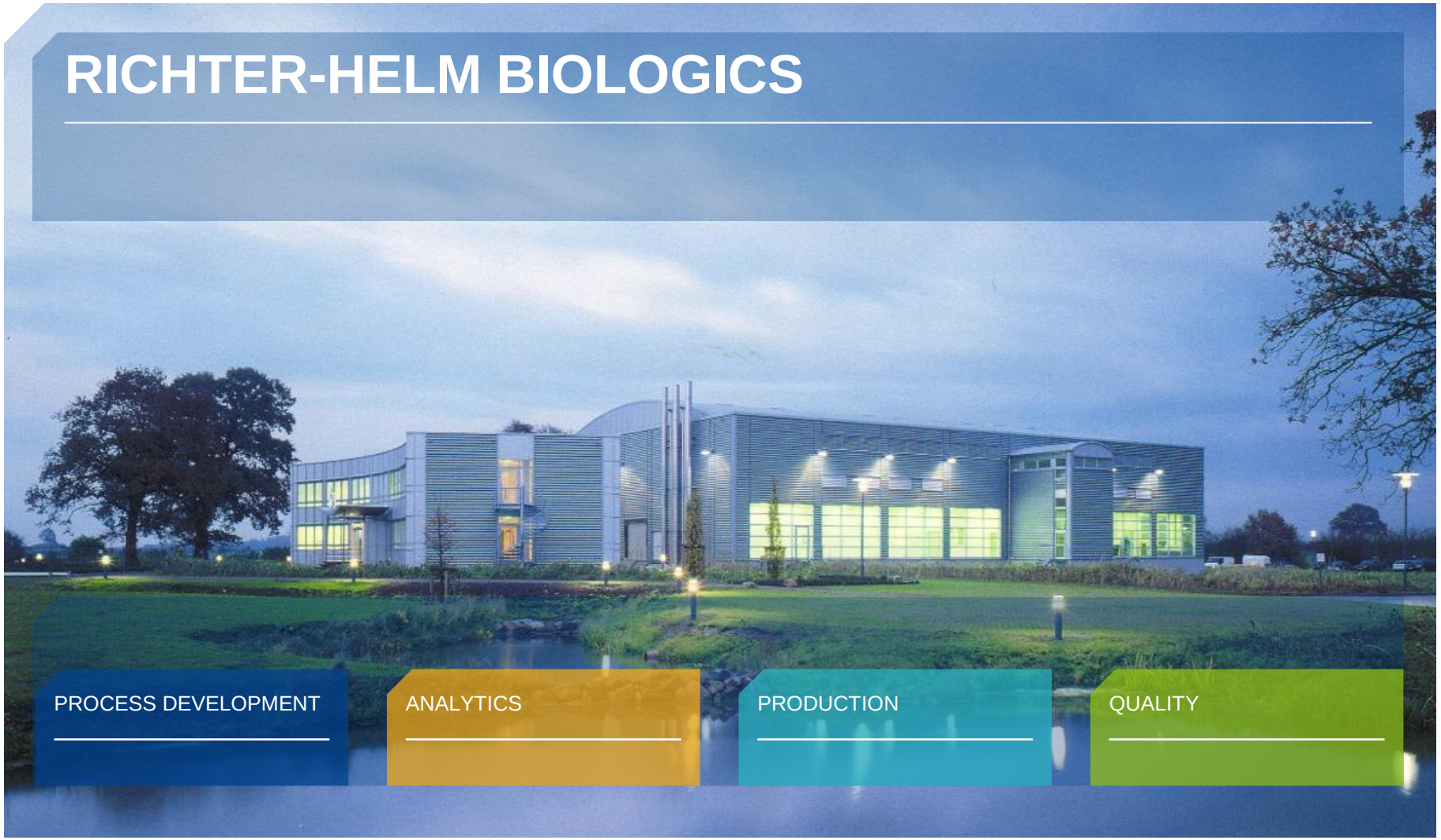
RICHTER-HELM BIOLOGICS



PROCESS DEVELOPMENT

ANALYTICS

PRODUCTION

QUALITY

RICHTER-HELM

AGENDA

HISTORY
COMPANY PROFILE
TECHNOLOGY AND SERVICES
SUMMARY

History of Richter-Helm - Owners Structure

Gedeon Richter Plc., Budapest, Hungary

- Richter sells APIs and finished form drugs to nearly 100 countries around the world
- Largest Hungarian pharma-ceutical company, today
- Turnover in 2018 was 1.4 billion €

www.richter.hu

HELM AG, Hamburg, Germany

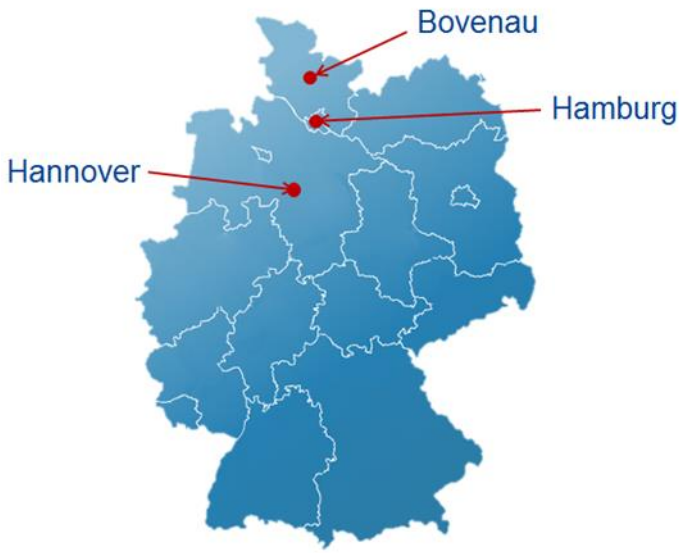
- World's leading independent chemicals and pharmaceuticals marketing enterprises
- Branches and sales offices in more than 30 countries
- HELM world-wide sales in 2018 were 8.3 billion €

www.helmag.com

History of Richter-Helm

More than 30 years of experience in biopharmaceuticals production

Our development and production facilities



1987	Foundation of Pharma Biotechnologie Hannover & start of GMP production
1989	Entering in contract GMP manufacturing
1998	Building up of development centre in Hamburg
2000	Construction of the large scale GMP facility in Bovenau
2003	Initiation of GMP production in Bovenau
2007	Acquisition by Gedeon Richter Plc and HELM AG
2009	Fully remodelled Hannover facility in operation
2011	Successful implementation of P. pastoris technology
2013	FDA approval
2014	Major capacity enlargement in Bovenau
2018	FDA approval

Our development and production facilities

Bovenau

Manufacturing Site up to 1500 L

Process Development
Analytical Development
Quality Assurance
Guidance

Hamburg

Headquarter & Development Center
Process Development
Quality Control & Quality Assurance
Business Development & Project Management
Administration

Hannover

Manufacturing Site up to 300 L

COMPANY PROFILE

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Experience and Potential Products

Richter Helm is focused on microbial production.

Production in Bacteria

- **Recombinant proteins** (e.g. cytokines, growth factors, antibody fragments)
- **Bacterial vaccines** (e.g. attenuated whole cell vaccines)
- **Plasmid DNA** (e.g. gene therapy, vaccines, starting material for virus production)

Production in Yeast

- **Recombinant proteins** (e.g. enzymes, new antibody formats)

RICHTER-HELM

Complete Drug Substance Development & Manufacturing from one Source

Biopharmaceuticals Production Value Chain

Locations and Services

Development centre, Hamburg

- Strain development
- Process development
- Analytical method development incl. bioassay development
- GMP compliant QC labs

GMP production plant, Hannover

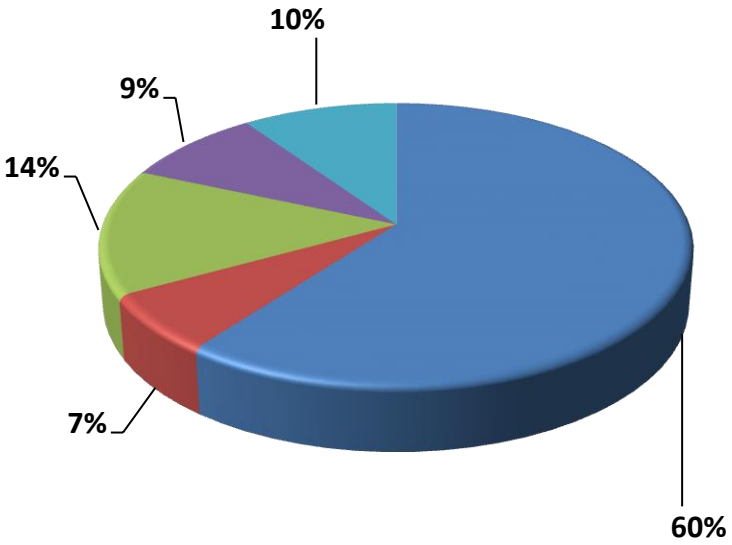
- GMP compliant multipurpose facility
- Manufacturing in up to 300 L fermenter scale
- 1000 m² production area
- Manufacturing license for proteins, DNA, vaccines and chemical conjugation

GMP production plant, Bovenau

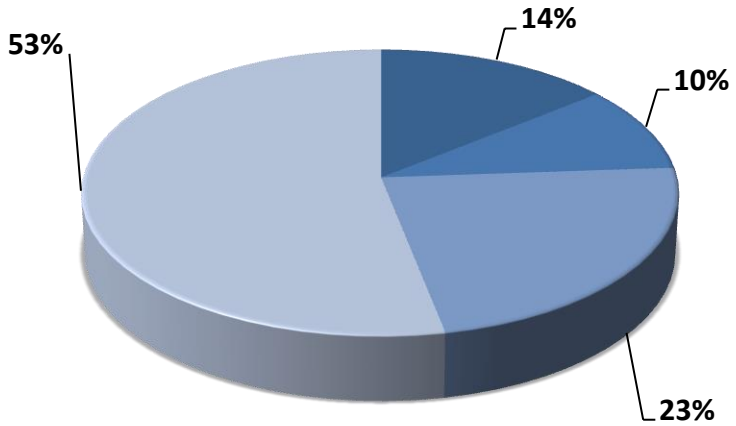
- GMP compliant multipurpose facility
- Manufacturing in up to 1500 L fermenter scale
- 4500 m² production area
- Manufacturing license for proteins, DNA and vaccines

Areas of Operation

Product classes by sales (since 2013)



Development Status of Manufactured Products by batches (since 2012)



Audit and Accreditation History

RICHTER-HELM

Employees


Highly skilled & motivated.
Headcount: 238
Hamburg: 106
Bovenau: 101
Hannover: 31

TECHNOLOGY AND SERVICES

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PROCESS DEVELOPMENT

SERVICES

- Strain development
- USP and DSP feasibility and optimization studies
- Development of fermentation and downstream processes
- Supply of preclinical materials
- Establishment of small-scale models
- Process characterization studies
- NOR and PAR studies
- Lifetime studies
- Impurity removal studies
- QbD and DoE experience

TECHNOLOGIES

- Various proprietary E.coli expression systems
- Bacteria and yeast cultivation
- Design of Experiments (DoE) modules
- Batch and fed-batch fermentation
- Cell harvesting by centrifugation, filtration, or TFF
- Broad refolding expertise
- Various conditioning technologies
- Ion-exchange, mixed-mode, HIC, RPC, and AF chromatography (FPLC, HPLC)

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ANALYTICS

SERVICES

- Phase-dependent method development and validation
- Regulatory compliant method transfer
- Establishment of reference standards
- Formal stability studies (ICH)
- Supportive stability studies
- Cell bank characterization
- Comparability studies

TECHNOLOGIES

- pH, visual Inspection, osmolality
- UV/Vis spectrometry
- U/HPLC (SEC, RP, IEX)
- Capillary electrophoresis (iCE3)
- 1D gel electrophoresis (Coomassie Brilliant Blue, silver staining, blotting, IEF)
- HCP and DNA quantification by the threshold system
- Generic and process-specific HCP-ELISA
- Quantitative PCR (rDNA, RNA, copy number determination)
- Cell-based bioassay (various readouts)
- Immunoassays
- Kinetic assays (e.g. of endotoxins, enzymatic activity)
- Receptor binding assays
- Flow cytometry

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PRODUCTION

PRODUCTION FACILITIES

- Two independent multiproduct facilities
- E.coli and yeast production systems
- Cell bank production (MCB and WCB)
- Fermenter volumes from 10 to 1.500 liters
- Flexible DSP scales
- Independent USP and DSP trains
- Technologies and equipment for biopharmaceutical production (e.g. methanol feeding for Pichia expression, preparative HPLC, large refolding vessels)
- Experience with diverse production technologies (e.g. enzymatic and chemical PEGylation, low-shear cell lysis, cell attenuation)
- A good balance of commercial and early phase projects

- Approved by all major regulatory bodies, including the FDA
- Well-established technology transfer procedures
- Man-in-plant (MIP) approach

QUALITY

QUALITY MEASURES AT A GLANCE

- Use of GMPs throughout every project: from clinical phases I, II, and III to commercial production, during manufacture, quality control, and storage of biotechnological intermediates, and drug substances
- Quality monitoring of all relevant processes
- A comprehensive quality manual
- A Document Management System for correct workflow, approval procedures and proper archiving of documents
- GMP certificate and manufacturing licenses from the responsible German authorities
- Facilities approved by regulatory bodies (including EMA, FDA, ANVISA, and MFDS)
- Five officially registered QPs

Summary

Expertise

- ✓ Strong track record in microbial production
- ✓ More than 30 years of experience in GMP production
- ✓ Trustful and continued customer relationships

Facilities

- ✓ GMP facilities approved by int. authorities
- ✓ Flexible production capabilities
- ✓ Extension of capacities planned

Customer Services

- ✓ Project Management
- ✓ Consultancy

Thank you!

RICHTER-HELM