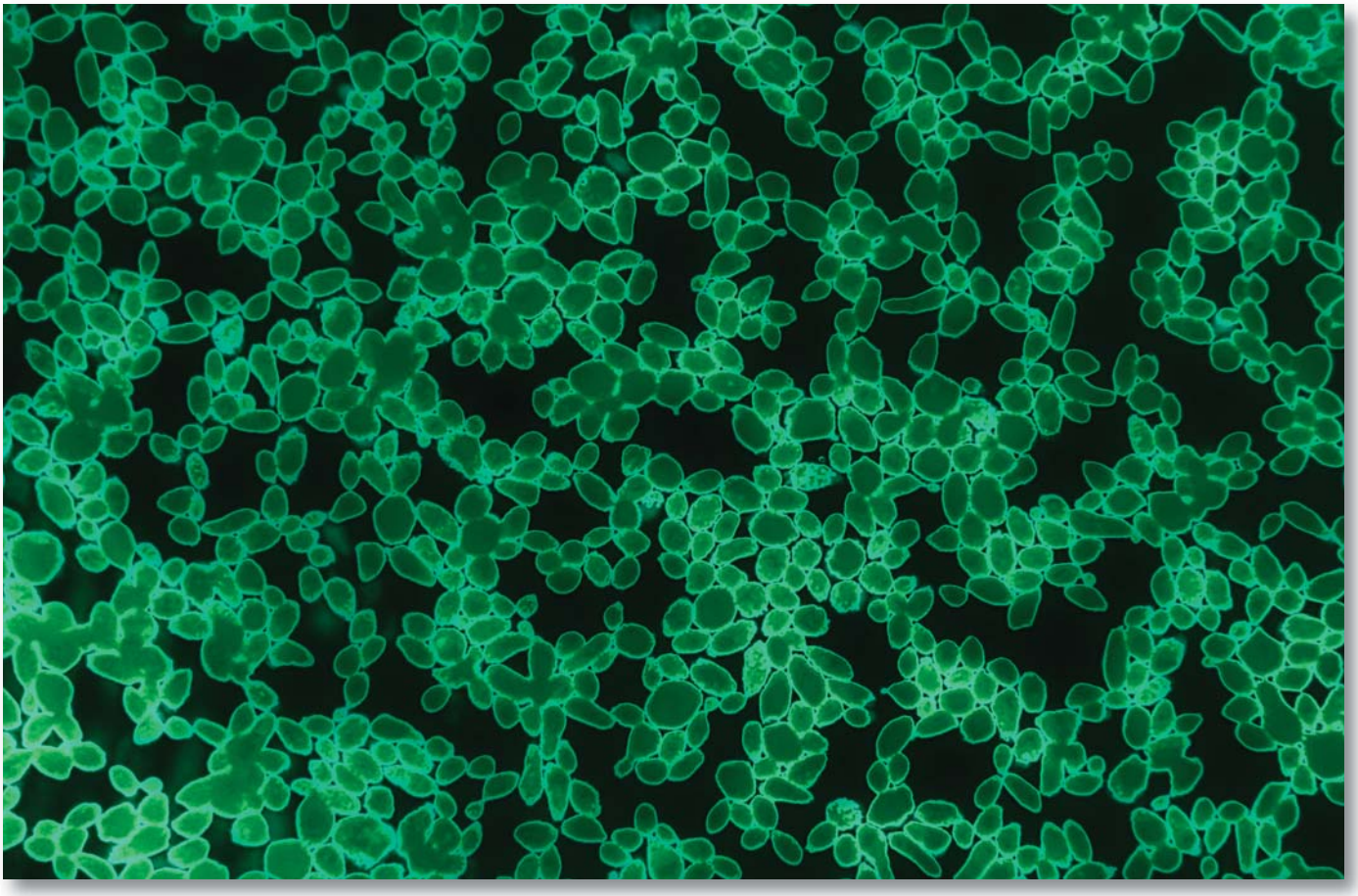
THE YEAST EXPERTS



Industry leading expertise in developing
yeast biomanufacturing processes

MSD

The expression of proteins in yeast can offer a number of advantages over other systems. MSD (formerly Avecia Biologics) has experience in developing manufacturing processes for more than 10 years in both *Pichia* and *Saccharomyces* which has given us an enviable track record from early phase clinical through to commercial manufacture.

Why yeast?

- Yeasts are able to secrete correctly folded protein into the culture supernatant
- Yeasts have the cellular machinery to accurately fold more complicated proteins than prokaryotic systems
- *Pichia* can use the methanol-inducible alcohol oxidase 1 gene (AOX1) which can result in tight control of heterologous expression
- Post-translational modifications are possible eg. glycosylation

MSD's track record spans >10 years' experience

R&D
15L - 100L

▶

Manufacturing trials
100L; 1000L

▶

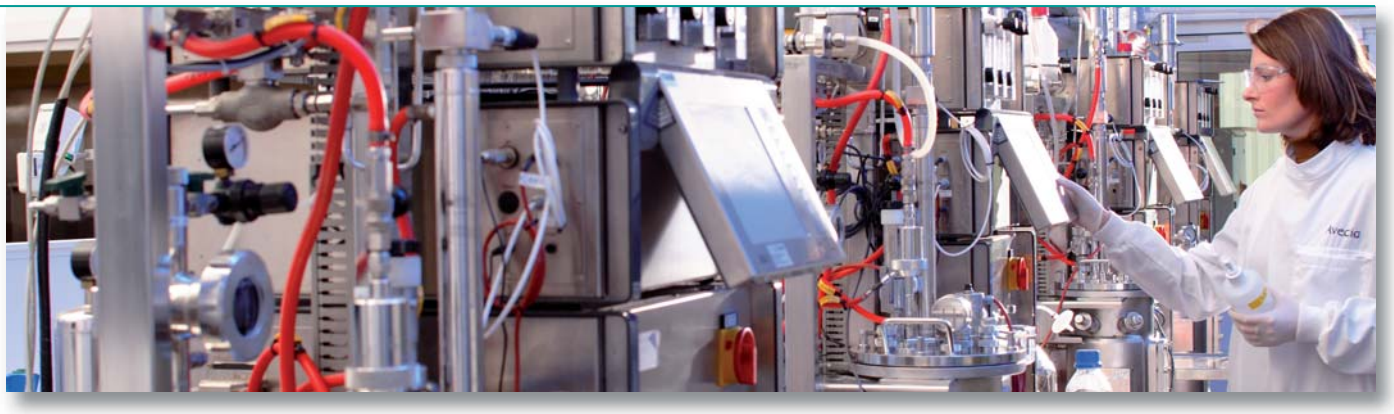
cGMP
100L; 1000L; 5000L

▶

Commercial manufacture
5000L

MSD's R&D capabilities

- 30 modern laboratory bioreactors capable of operating high cell density yeast processes with methanol and O^2 supplementation
- Experience using FMEA methods to define Laboratory Process Characterisation (LPC) studies ahead of validation
- LPC studies carried out using statistical experimental design, allowing rapid and robust process characterisation
- Experience of scaling fermentation processes from 15L laboratory to 5000L production scale
- Developed yeast processes from Phase I through Phase II/III/Validation to NDA and commercial manufacture
- Experience of scaling expanded bed chromatography from 2.5cm to 100cm production scale



MSD's manufacturing capabilities at Billingham

Upstream

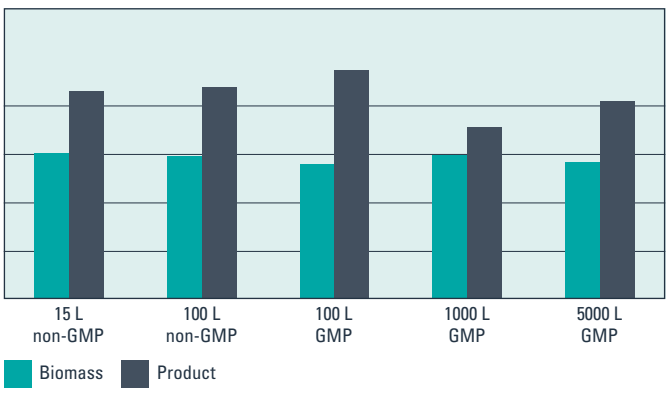
Our manufacturing capabilities are designed to enable:

- The high oxygen transfer rates and cooling capacities required for high cell density culture
- Reproducible and robust scale up from 15L laboratory scale to 5000L manufacturing scale
- Delivery of consistent performance at all scales

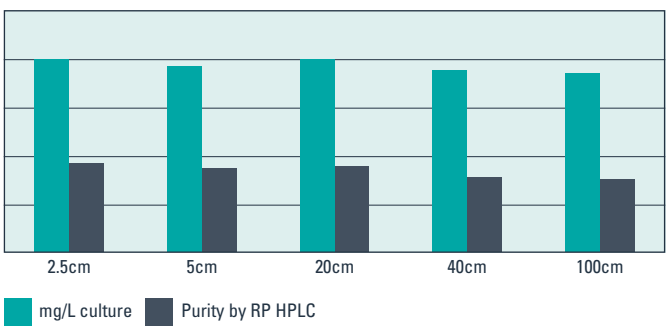
Downstream

- Able to apply the full range of separation and purification options including the use of expanded bed chromatography (EBC)
- Extensive experience of EBC capture/purification:
  - Provides rapid and efficient scalable primary capture combined with initial purification
  - Excellent scale-up data from a 2.5cm expanded bed up to 100cm
  - Taken through commercial manufacture

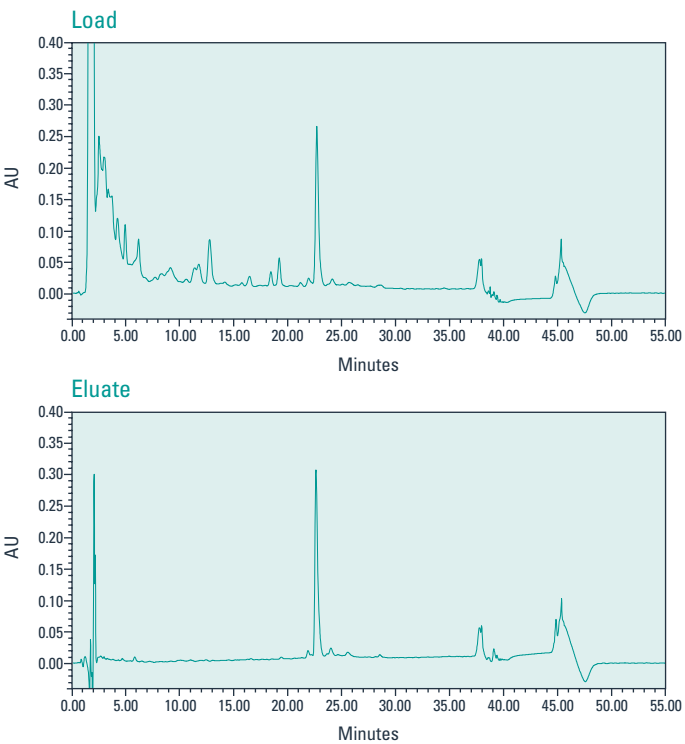
Final biomass and product titres



EBC - yield and purity



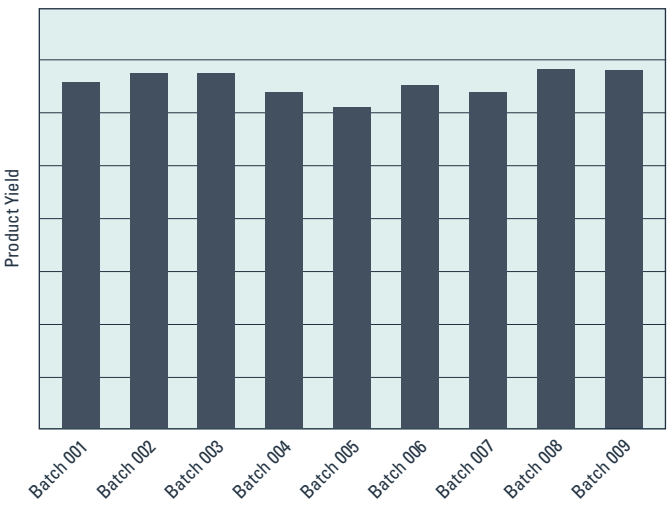
Analytical RP-HPLC of EBC load and eluate from 5000L run



MSD - the yeast experts

- Our capability in process development and biomanufacturing have been shown to result in robust reproducible yeast-based processes
- More than 10 years' experience in producing clinical therapeutic proteins using yeast systems
- Successful track record in taking processes from early phase clinical through to late phase and commercial manufacture
- Able to demonstrate consistent cGMP performance and ouput
- Strategic investment in technology advances to deliver further improvements in performance, output and cost-of-goods

Yeast process (*Pichia*) consistency at 1000L GMP scale



MSD Biologics (UK) Limited

PO Box 2
Belasis Avenue
Billingham TS23 1YN
United Kingdom

Tel: +44 (0) 1642 363511
Fax:+44 (0) 1642 364463

Email: msdbio@merck.com

www.msd-uk.com/bmn

MSD

April 2010.