High-Tech Production of Innovative Medicines

Roche's Expertise in Biotech Manufacturing

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Manufacturing therapeutic proteins

Challenges facing the pharmaceutical industry

- Ensure adequate production capacity across the industry to cover future needs
- Capital investment in biotech manufacturing technology is more costly than in classical chemical production
- Essential to get the process right for every single product, right from the beginning – i.e. as early as technical development
- Experience in biotech manufacturing will be a competitive advantage in the pharmaceuticals market of the future

Therapeutic drugs

Extraction from plants or animals

"Modern" biotechnology

Conventional synthesis

Rational drug design

Combinatorial chemistry

Natural products

Biopharmaceuticals (high molecular weights)

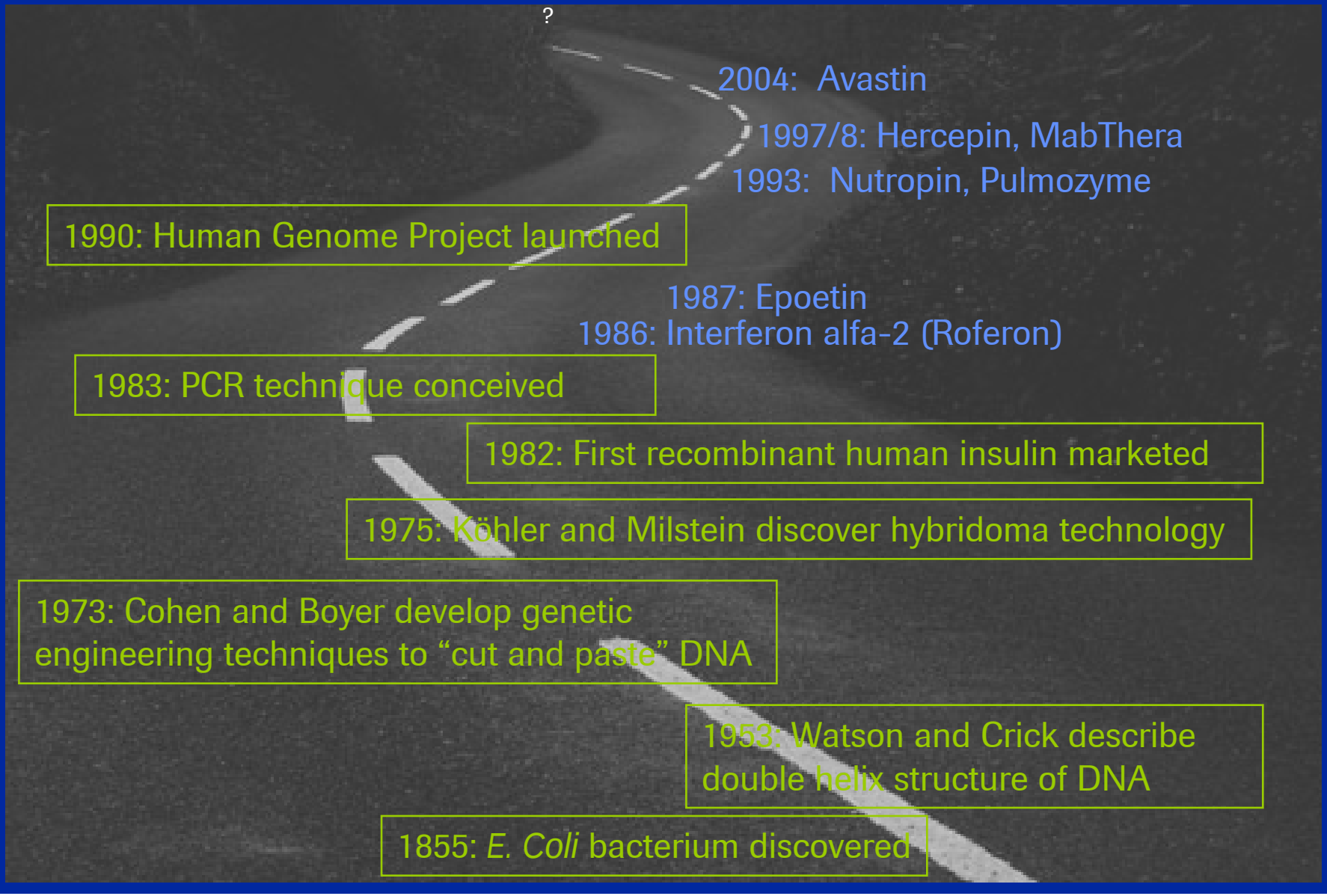
Synthetic products (low molecular weights)

Morphine, Chinine

Proteins, i.e. EPO, Herceptin

Xenical, Xeloda

Some important milestones



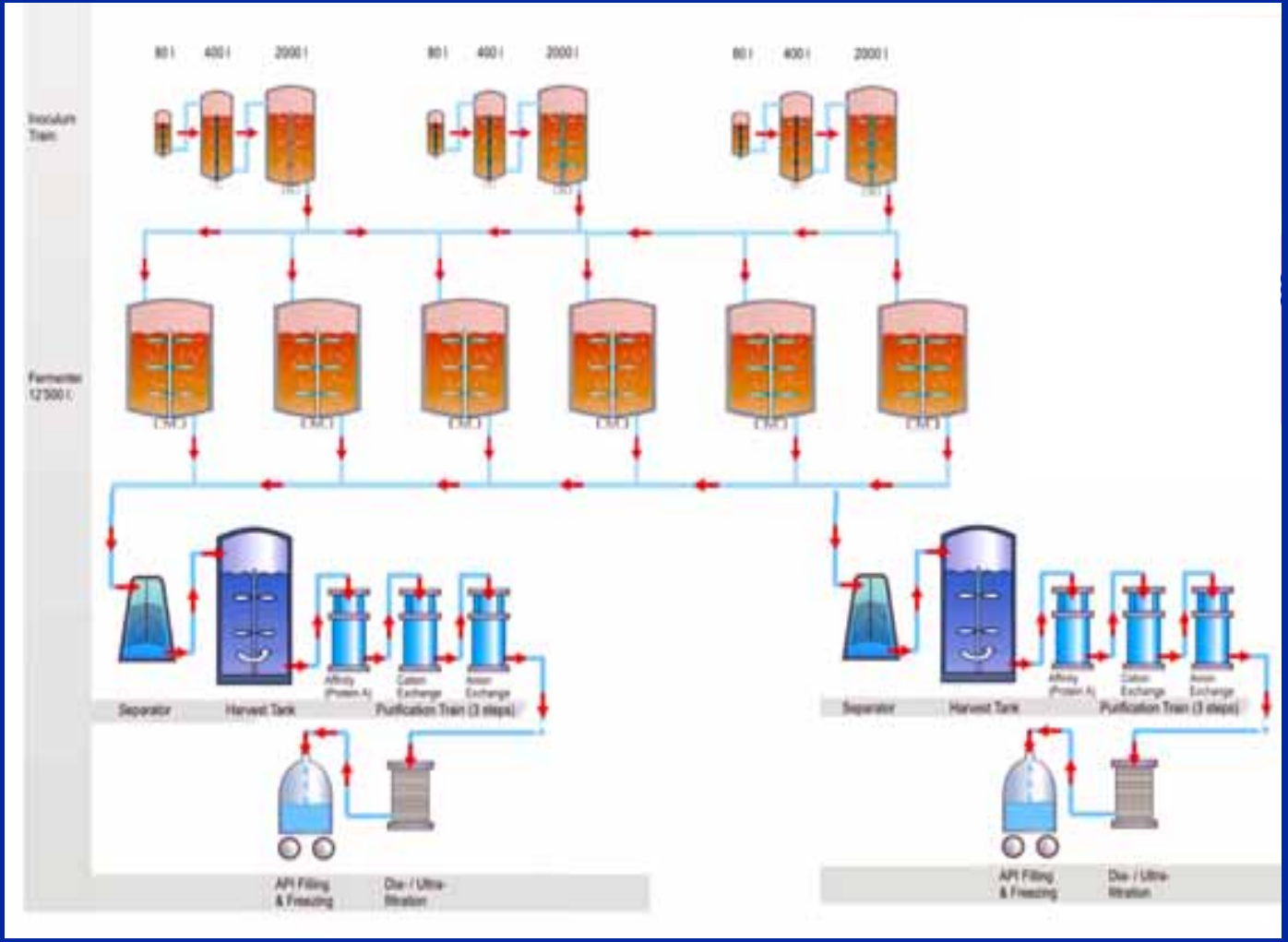
High molecular weight protein or low molecular weight product – does it make a difference for manufacturing?

Difference between chemical manufacturing and biotech production

	Chemical production	Biotech production
The manufacturing process	Synthesis: Organic solvents, highly reactive components Wide temperature and pressure variety	Fermentation process, cells or bacteria produce the active pharmaceutical ingredient Very narrow pressure and temperature range Specific downstreaming process
Products manufactured	Small molecules	Large molecules, protein structure
Production facility	Closed reaction, open space	Highly contained environment
Safety & environment	Organic solvents pose higher risk	Water + cells
Sterile condition	Seldom	Yes!
Dilution factor	Low	High

Biotech manufacturing facility

Production of Active Pharmaceutical Ingredients



Inoculum

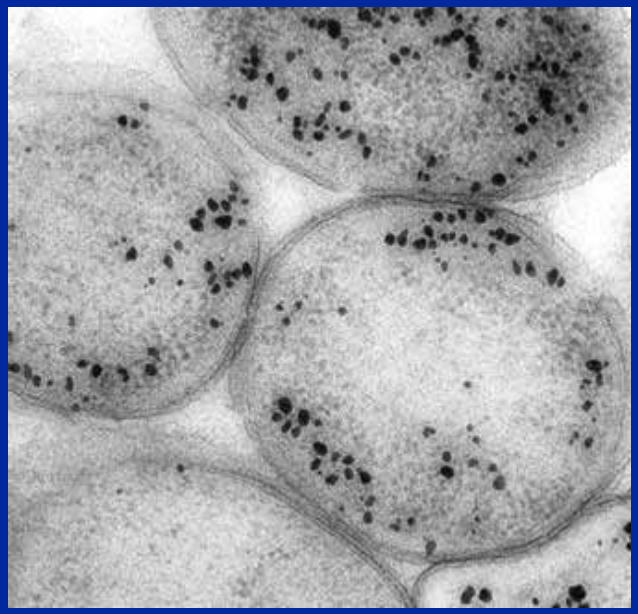
Fermentation

Purification

Filling

Large-scale biotech production

Essentials



1. Production cells

2. Large-scale production technologies

Large-scale biotech production at Roche

The basis

Microbiological production (*E. coli*)

→ **Manufacture of plain protein products**

→ **Fast growing cells (20 min)**

- Reteplase
- Interferon (Roferon, Pegasys)

Production by mammalian cells

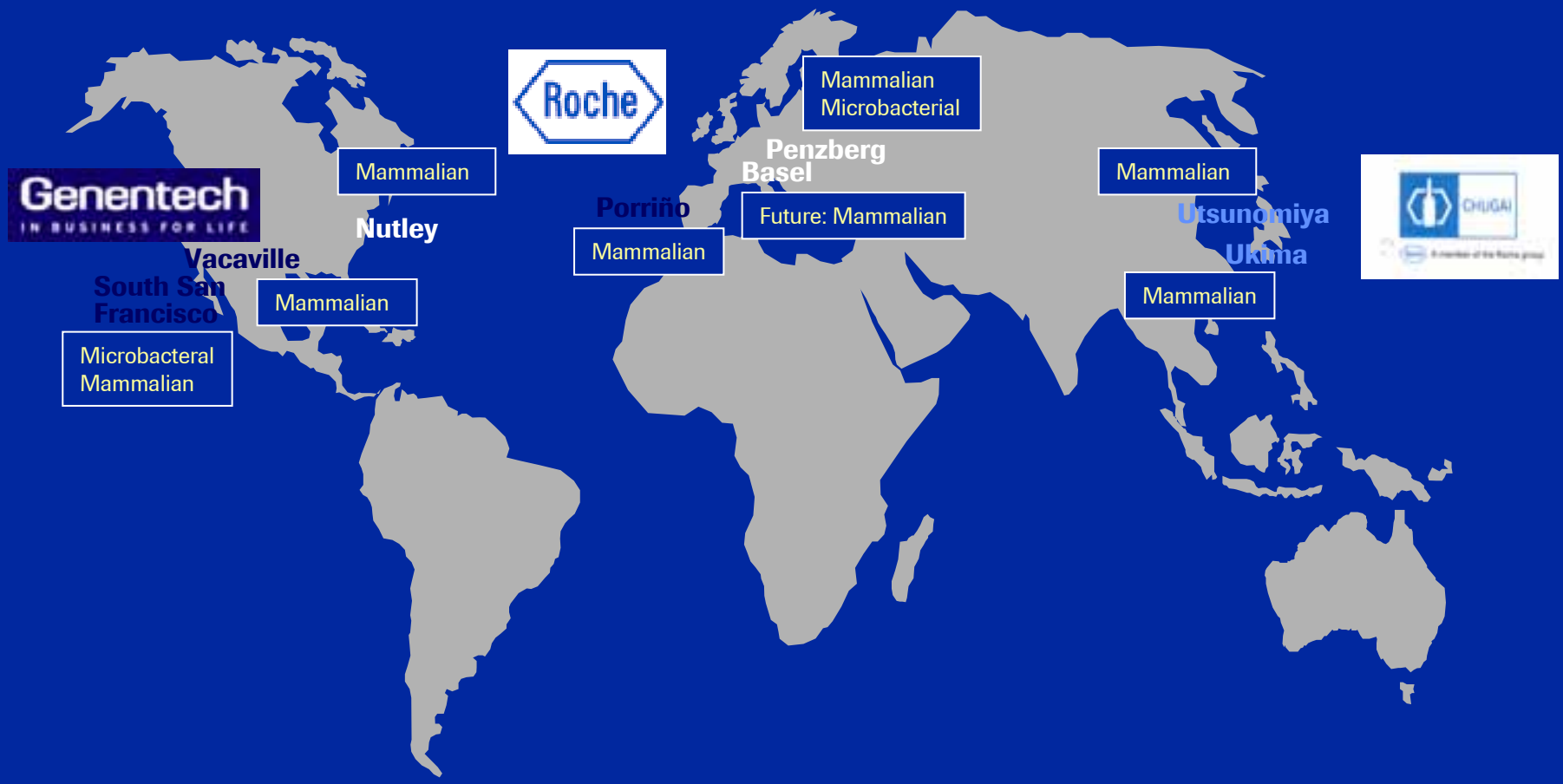
→ **Manufacture of complex protein products, e.g. sugar side chains**

→ **Slow growing cells (24h)**

- Erythropoietin (NeoRecormon)
- Monoclonal Antibodies:
  - Rituximab (MabThera/Rituxan)
  - Trastuzumab (Herceptin)
  - Bevacizumab (Avastin)
  - Daclizumab (Zenapax)

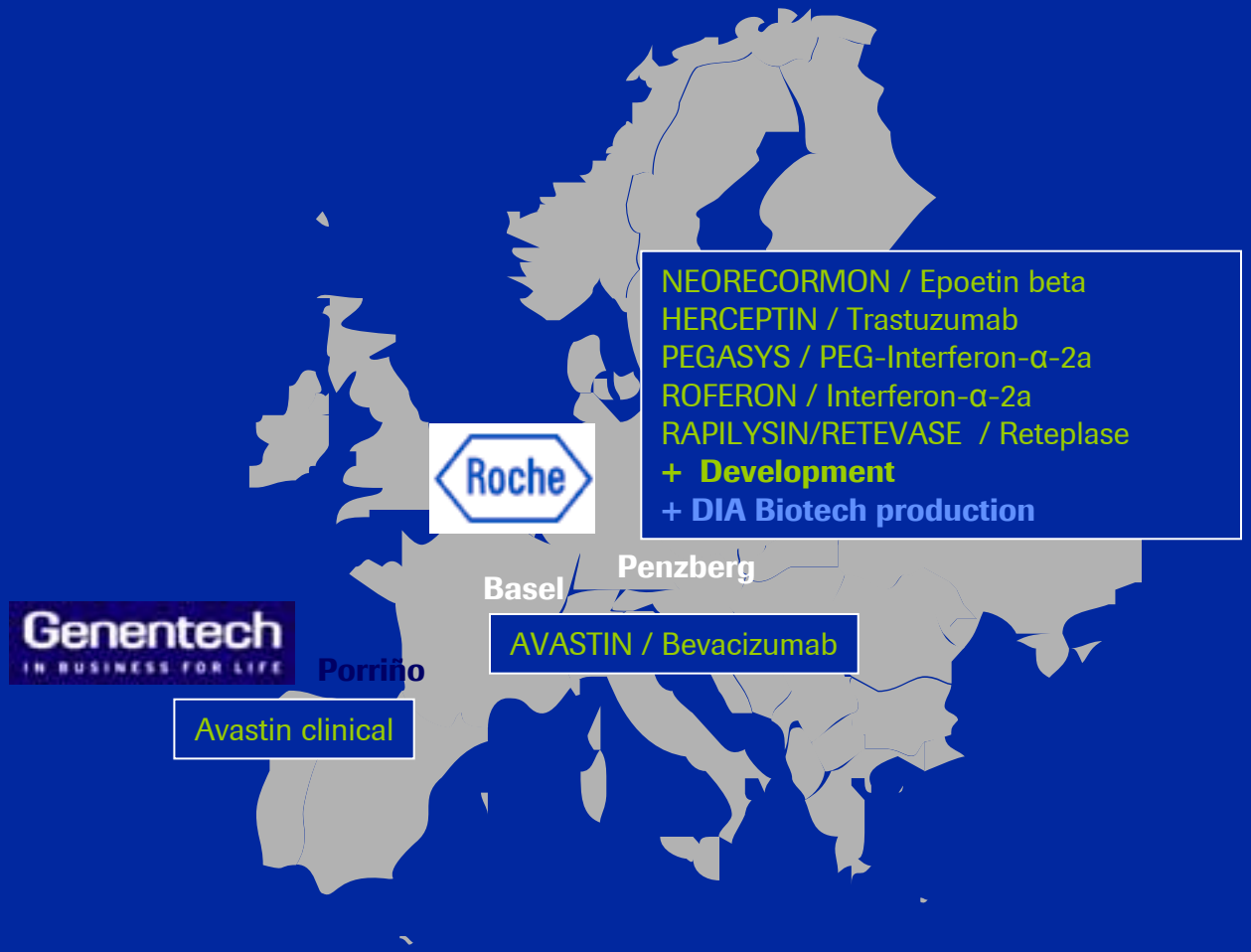
Roche Group biotech production sites

Worldwide distribution



Roche Group

Biotech products manufactured in Europe



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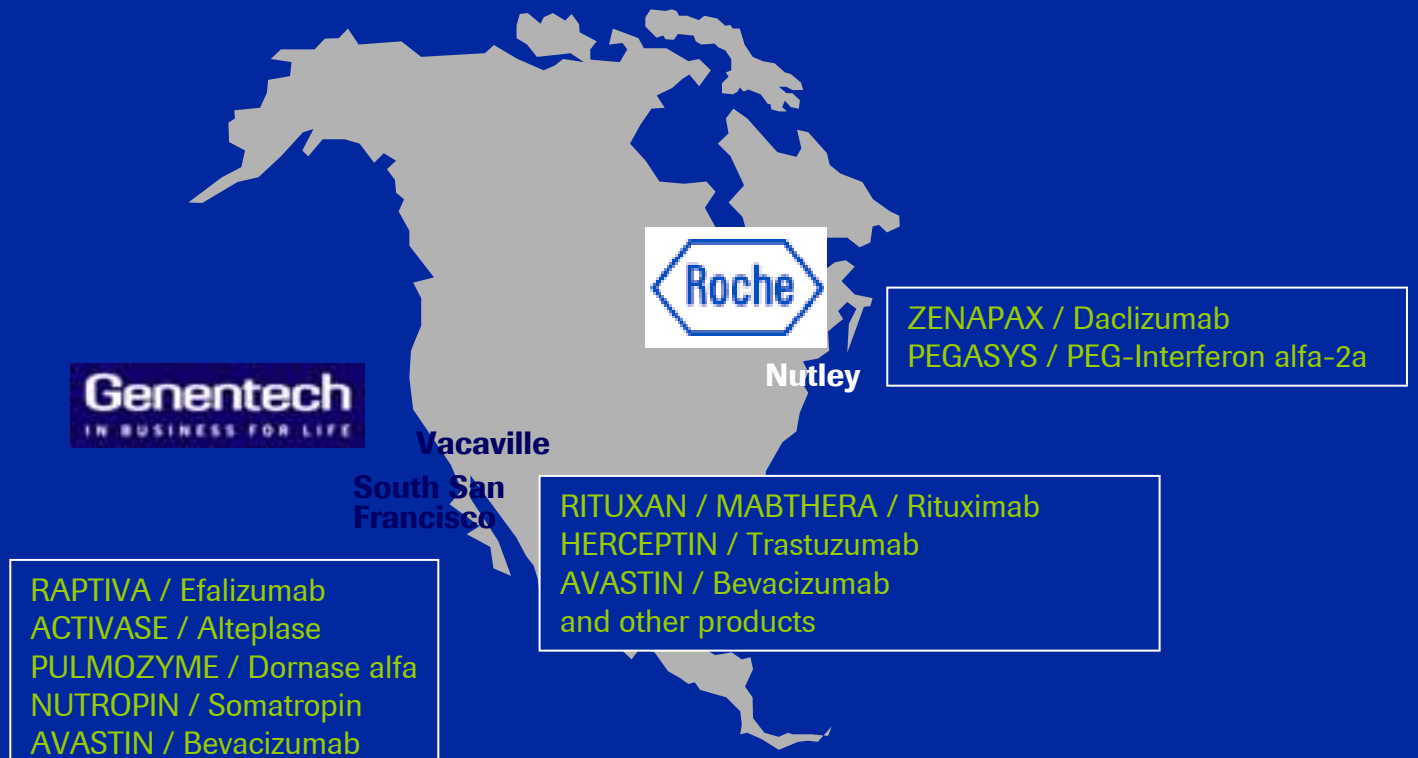
Biotech products manufactured in North America



ZENAPAX / Daclizumab
PEGASYS / PEG-Interferon alfa-2a

RITUXAN / MABTHERA / Rituximab
HERCEPTIN / Trastuzumab
AVASTIN / Bevacizumab
and other products

RAPTIVA / Efalizumab
ACTIVASE / Alteplase
PULMOZYME / Dornase alfa
NUTROPIN / Somatropin
AVASTIN / Bevacizumab
and other products

Roche Group

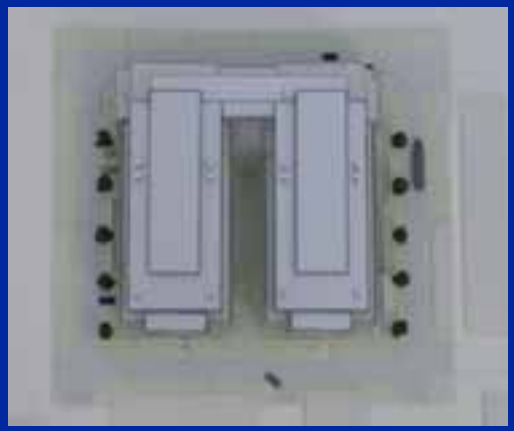
Biotech products manufactured in Asia

The future lies in biotech –
Roche continues to invest …

The Roche Basel MAB project

- New building at Grenzacherstrassse by architects Herzog & De Meuron
- Multipurpose plant with fermentation capacity of 6 x 12,5 m^3 and 2 downstreaming lines
- 150 new jobs created
- Investment of CHF 400 m over 3 years
- Groundbreaking currently ongoing construction due to start Q1 2005
- Facility qualification and approval process due to start in 2007
- First market supply planned for 2009
- Products: bevacizumab (active ingredient of Avastin) and other biotech development products

The Roche Penzberg Biologics IV project



- New building housing multipurpose plant with fermentation capacity of 6 x 12,5 m^3 and 2 downstreaming lines
- 150 new jobs created
- Investment of CHF 400 m over 3 years
- Groundbreaking currently ongoing
- Facility qualification and approval process due to start in 2007
- First market supply planned for 2009
- Products: trastuzumab (active ingredient of Herceptin)

The Roche Group is maintaining its leadership in biotechnology in a fast growing environment