

BioStart : Manufacturing and operations in Biotech

Strategic stakes and technology evolution in recombinant protein production

APFL

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Triskel: a strategic consulting firm for biopharmaceutical companies

- Provides high quality, integrated and **customized strategic expertise**
- Crafts innovative development plans and negotiates effective **regulatory strategies**
- Implements **development plans** working through Steering Committees with the client to guide and monitor CMO's, CRO's or other development partners
- Encompasses all expertise necessary to **register medicinal products** in European and US markets

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Brief history of recombinant protein production

1953 : Watson, Crick and Franklin elucidate the DNA structure

1957 : Watson and Crick establish the current model of protein expression

1961 : Nirenberg and Khorana decipher the genetic code

1973 : Cohen and Boyer insert the first recombinant DNA (insulin) in E.Coli

1975 : Köhler and Milstein make the first Hybridoma

1976 : Swanson and Boyer create Genentech

1978 : The 1st recombinant protein (*h.* Insulin) is produced at Genentech

1996 : Dolly, by Campbell

1982 : Approbation of r. Insulin (licenced to E. Lilly)

1987 : 1st recombinant protein in CHO is approved (tPA - Genentech)

2006 : Approbation of the first transgenic rec. protein (AT III in goat, by GTC)

Cell therapies and genome repair will not be evoked in this presentation, dedicated to recombinant proteins

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Strategic stakes and technology evolution in recombinant protein production

- **A few data**
- **Technology evolution in the past 20 years**
- **State of the Art**
- **Near future and trends**
- **Analysis**
- **Conclusions**

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The Pharmaceutical market in 2006

- Marché Pharma 2006 : 643 \$ BN*, of which the recombinant drugs count for about 15 %

* source : IMS MIDAS

#	Trade name	sales (\$BN)	Growth 06/05
1	Lipitor (atorvastatin)	13.6	4.2 %
2	Nexium (esomeprazole)	6.7	16.9 %
3	Seretide /Advair (Fluticasone + salmeterol)	6.3	10.3
4	Plavix (clopidrogel)	5.8	-3.4
5	Norvasc (amlopidine)	5.0	-0.5
6	Enbrel (Etanercept)	4.5	18.4
7	Zyprexa (olanzapine)	4.7	-0.4
8	Risperdal (risperidone)	4.6	12.3
9	Aranesp	4.1	26
10	Effexor (venlafaxine)	4.0	2.7

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Top 10 Therapeutic class 2006

No	Class of Products	2006 sales [US bin \$]	Selected Products
1	<u>Erythropoietins</u>	11.94	Aranesp,Procrit,Epogen,Neo-Recormon,ESPO
2	Major Cancer Antibodies	10.62	Rituxan/Mabthera,Herceptin,Avastin,Erbitux,Vectibix
3	Anti-TNF Antibodies	10.28	Enbrel,Remicade,Humira
4	Insulin & Insulin analogs	8.97	Humalog,Humulin,Lantus,Levemir,Novorapid,Actrapid,Novolin
5	Rec. <u>coaqulation</u> factors	4.71	Novoseven,Kogenate,Helixate,Refacto,Advante,Recombinate,Benefix
6	<u>Interferon beta</u>	4.40	Avonex,Rebif,Betaseron/Betaferon
7	G-CSF	4.36	Neulasta,Neupogen,Neutrogin,GRAN
8	Human Growth Hormone	2.47	Genotropin,Norditropin,Humatrope,Nutropin,Saizen,Serostim
9	Interferon alpha	2.26	Pegasys,Peg-Intron,Intron-A
10	<u>Enzyme Replacement</u>	1.7	Cerezyme,Fabrazyme,Aldurazyme,Myozyme,Replagal,Naclazyme,Elaprase

*according to LaMerie Business Intelligence, February 2007

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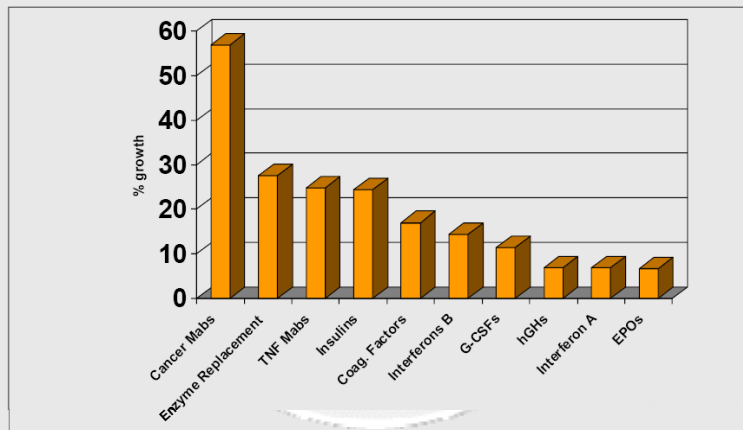
Top 10 biopharma sales 2006

No	Product	2006 sales [US bln \$]	MoA	Class of compound	Company
1	Enbrel	4.47	TNF-alpha	Fusion AB	Amgen/Wyeth
2	Aranesp	4.12	EPO-R	Hu epo alpha	Amgen
3	Rituxan	3.91	anti-CD-20	r-Mab	BIIB/DNA/Roche
4	Remicade	3.76	TNF-alpha	r-Mab	Centocor/S-P
5	Procrit	3.18	EPO-R	Hu epo alpha	J&J
6	Herceptin	3.17	HER-2	r-Mab	DNA/Roche
7	Epogen	2.84	EPO-R	Hu epo alpha	Amgen&Kirin
8	Neulasta	2.71	CSF-receptor	PEG GCSF	Amgen
9	Astrapid/Novolin/Mixtard	2.65	Insulin receptor	r Hu Insulin	NovoNordisk
10	Avastin	2.39	V-EGF	r-Mab	DNA/Roche

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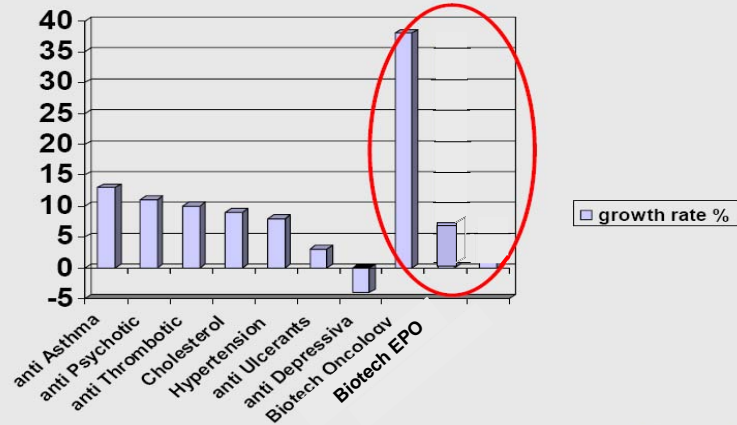
Class growth rate 2006/2005 in Biotech



*according to LaMerie Business Intelligence, February 2007

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Drug class growth rate in Pharma



*according to LaMerie Business Intelligence, February 2007

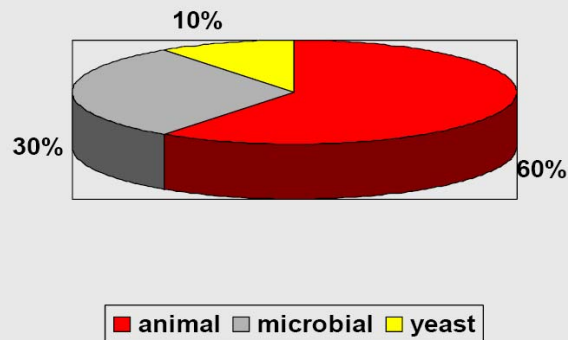
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Majority of Biotech products made in Animal Cells



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20 year of cell culture improvement

- Early years 87-90's
- Evolution 90's -2005
- Current state of the art
- Trends for the future

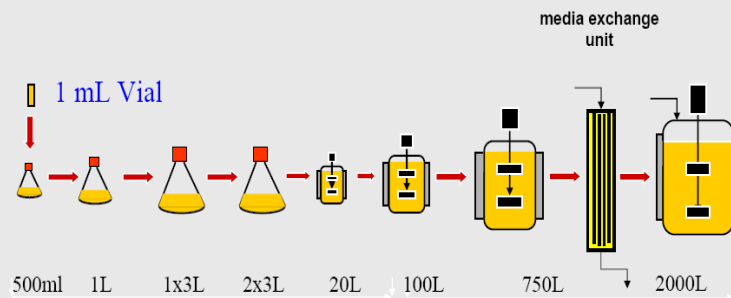
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Early years 85-90's

- Serum-based processes [~ 5% fetal BSA]
- Product titers in the range of ~ 5→200 mgs / L, a few had > 500 mg / L
- Low efficiency “downstream process” [20→30%...]
- analytical methods for characterization & release just “ok”
- vial as the major therapeutic application form for therapeutic application
- Regulatory submissions ... [“ok”]

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Early years 85-90's

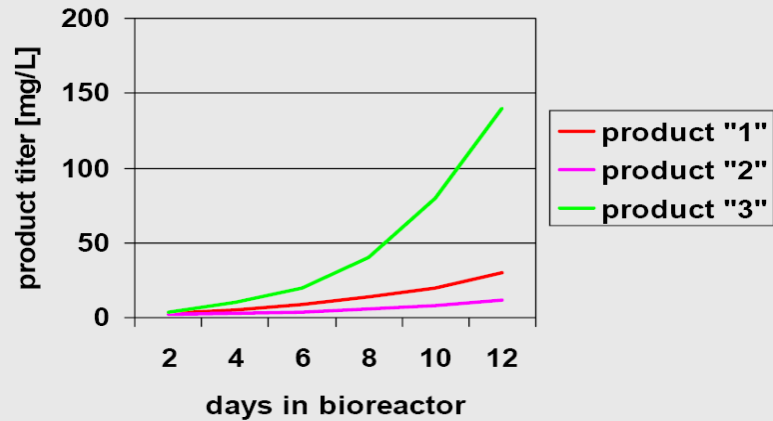


Overall Time from vial to Harvest ~ 42 days

Typical cell concentration at harvest : 5×10^6 cells/ml

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Early years 85-90's



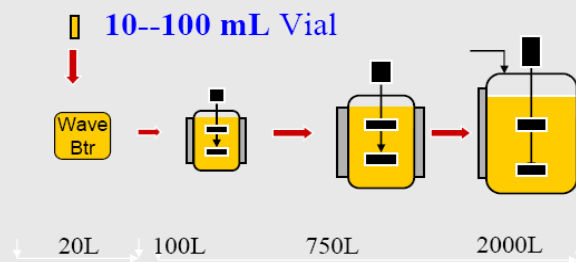
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Evolution 90's - 2005

- Chemically defined media !
- Product titers in the range of $\sim 1 \rightarrow \underline{5}$
- Straight-forward "platform downstream process" [$> 50\%$ recovery]
- Extremely elaborate and precise analytical methods for characterization & release
- Many "convenience-related" application forms for therapeutic use
- Regulatory submissions much more standardized and outcome predictable...

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Evolution 90's - 2005



Overall Time from vial to Harvest ~ 22 days

Cell density at harvest > 10^7 cells/ml

Rational fed batch process (supply of depleted nutrients only)

Continuous processes reach the industrial scale

Process scale up to 10 000 L

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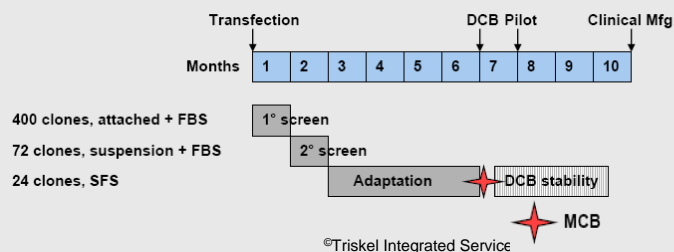
Current state of the art Production

- Bioreactor size up to 20 000 L
- Cell concentration reach 5-10 x 10 exp7 cells /ml in fed batch
- Records of 10 g/L (Mabs) reach at pilot scale
- Strong development of disposable technology (wave bags and ion- exchange membranes)

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Current state of the art Development

- 1 year from pre-MCB to First in Man !
 - Includes assay development, process development, and tech transfer !
 - Requires highly integrated CMC teams
 - Regulatory agility
 - Requires very flexible partners (Fill and Finish, CMO)
- 10 months from transfection to clinical manufacturing !



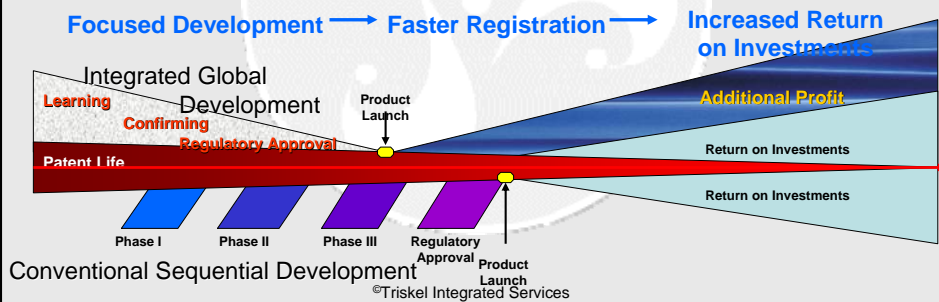
Debottlenecking

- **Administrative delay from regulatory authorities must be anticipated**
- **Very frequent internal bottlenecks:**
 - Contract signature delay with CMO's or CRO's (often 6 months...)
 - Analytical teams understaffed or tools not in place:
 - Detailed structural characterization by MS
 - Assessment of aggregation by AUC and LS
 - On line analytical technology (PAT..)
 - External audits not anticipated
 - Stability studies requirement not anticipated
 - Approval from ad hoc internal committees which meet every other month.

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The Triskel concept

- **Focus on time to registration rather than speed to market**
- **Proof of concept (POC) more relevant than FIM**
 - 2 clinical sequences rather than 3
 - POC from Phases I/II combined in 1 or 2 clinical trials with clinical batches produced in one shot from a CMO
 - Phases II/III after process optimization
 - Regulatory agility
 - More time initially for CMC saves time for registration



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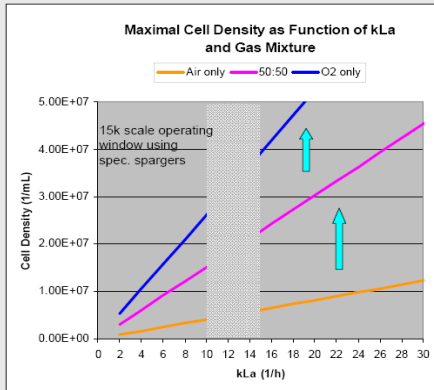
Short terms improvement in industrial cell culture

- Improvement via molecular biology
 - Reduce apoptosis through insertion of apoptose reducing genes (bcl-2 genes for instance)
 - Percivia PER. C6 cell line is derived from a single, human healthy cell line, genetically modified to replicate indefinitely. Current record is 15 g/L of MAb (March 08)
- Improvement via cell culture technology
 - Goal : increase cell density to increase protein recovery
 - Systematic review of all parameters through high throughput tools: selection of surfactants, Design of Experiments for medium optimization..)
 - Scale-up optimization

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Short term technological improvements: 10 g/L in CHO

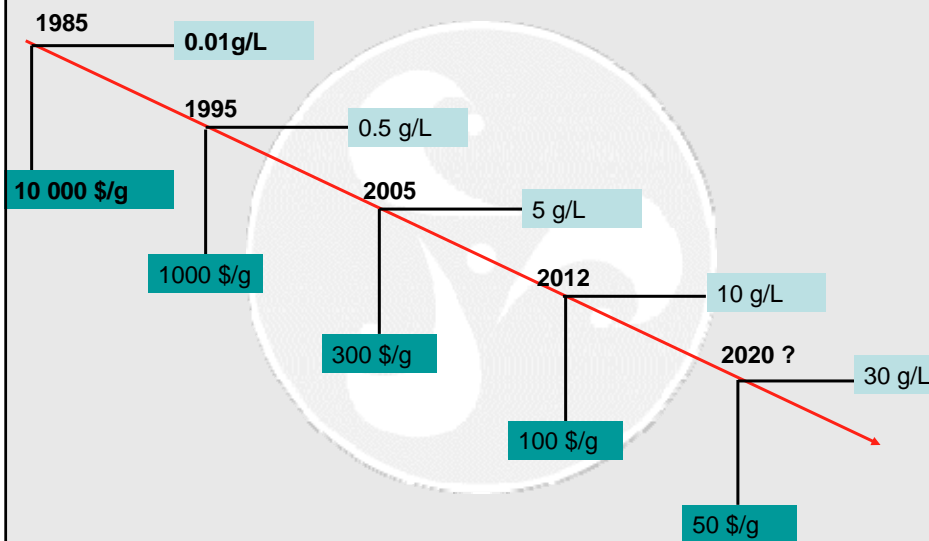
- Better understanding of cell physiology
 - Rational feeding rather than medium exchange
 - Prolong culture longevity at the plateau
 - 10 g/L = 50 pcd x 40 exp 6 cells/ml x 5 days



Oxygen sparging allows to reach 30-40 exp 06 cells/ml

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Impact of innovation on production cost



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A changing environment requires a changing development strategy (I)

- **Late 80's : very few biotech product licenced**
 - Regulatory constraints “negotiable”
 - Relatively few clinical trials necessary
 - Low attrition rate (low risk of clinical failure)
 - Financial output relatively predictable
 - Pipe-line fed by many ideas and products
 - Development cost “affordable”
 - Limited spread of the Technology
 - Cost of health not yet at concern

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A changing environment requires a changing development strategy (II)

- **2008 : Many biotech products licenced (>50)**
 - Spread technology (India, China...)
 - Regulatory guidances published : more stringent process
 - Clinical trials all over the world have to be prepared
 - Attrition rate increasing
 - Expectations from shareholders higher and higher (gross margin > 90%)
 - Shortage of new molecules
 - Despite optimistic claims, the duration of development is not decreasing (about 10 years)
 - Development cost reach summits (50 000 K€)
 - New facility costs are now about 10 000 \$/m²
 - Cost of health issue

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Strategy for the development of a new company

1. Have your first product developed → go to a CMO for Manufacturing
2. Have your product on the market → continue manufacturing at the CMO and grow your pipeline
3. Build your facility only when you can fill it with your production. Consider a GMP pilot plant if the portfolio justifies it
4. Multiply the partnerships

Alternative : sale after Proof Of Concept !

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