BIOPHARMACEUTICALS
Availability, Diffusion, Sustainability

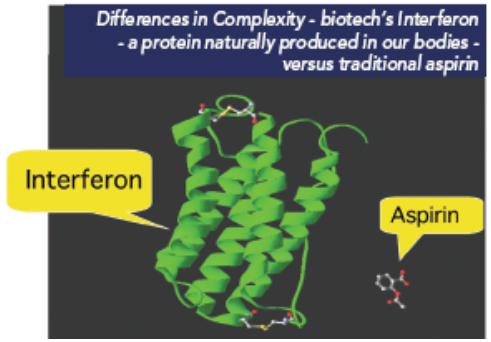
Massimo Riccaboni
University of Florence & CERM, Rome

The need for a precise definition of “biopharmaceutical” products

Since the 1980s, the general consensus seems to be that biopharmaceuticals are a class of therapeutic products produced by modern biotechnological techniques (recombinant DNA and hybridoma technology) that is to say therapeutic proteins synthesized in engineered biological systems.

Walsh (2002) proposed the following definition:
“*A protein or nucleic acid based pharmaceutical substance used for therapeutic or in vivo diagnostic purposes, which is produced by means other than direct extraction from a native (non-engineered) biological source*”

Classification Criteria



Product characteristics:

large vs small molecules (molecular weight, structural complexity)

Production process:

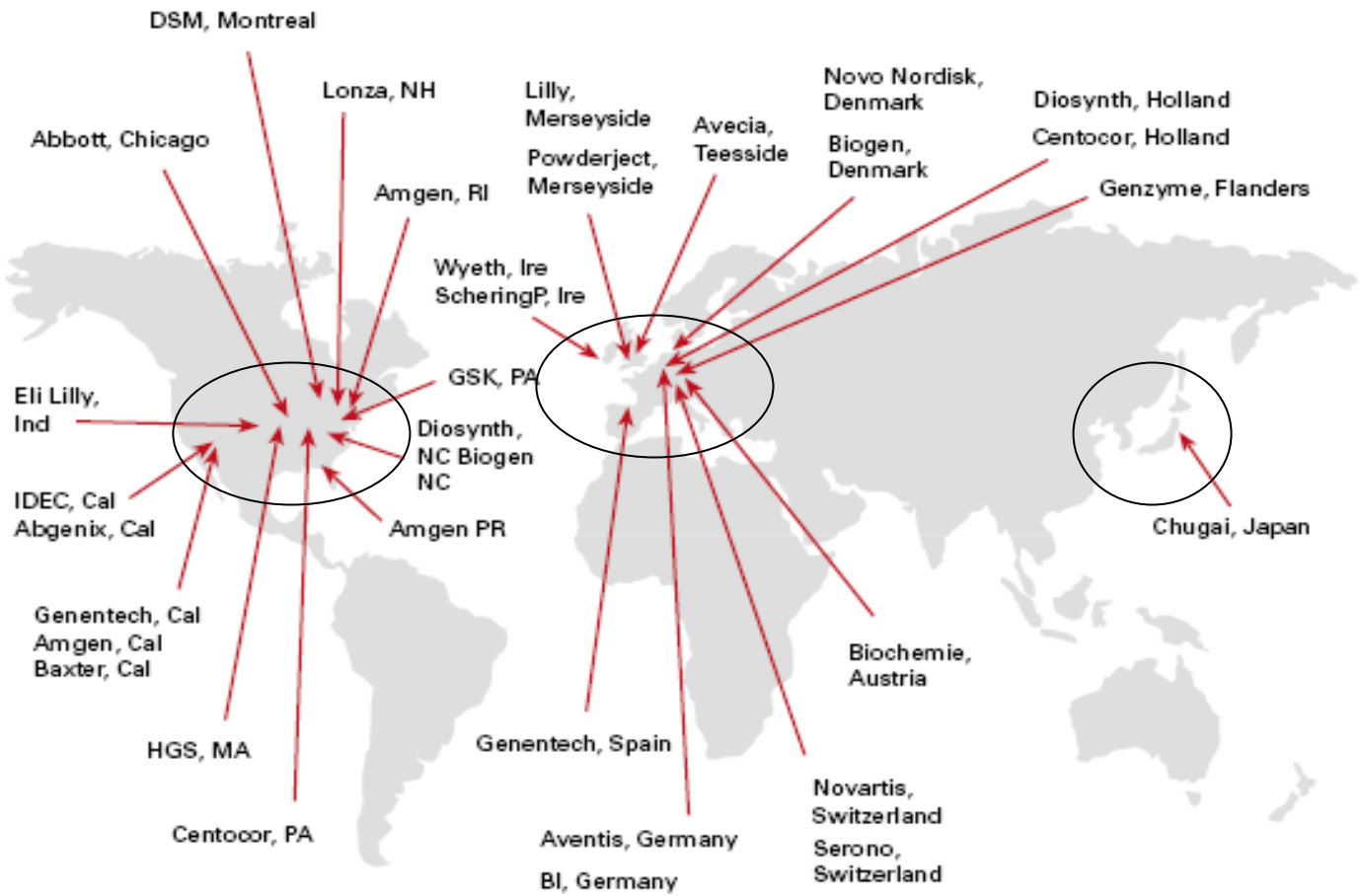
bioprocessing vs chemical synthesis

Source?

The definition of ‘product’ is inseparable from its production ‘process’ and manufacturing operation. This close linkage between ‘product’ and ‘process’ means there will not be a quick advent of low-cost alternatives or biogenerics and implies capacity-constraints.

The same biologic drug, manufactured through the same series of steps, at two different locations can have different pharmacokinetic profiles!

The location of biopharmaceutical production



Source: Avecia and BioPharmServices. Map shows location of the majority of bioprocessing companies (recent bioprocessing investment of > $50 million +) disclosed publicly.

Off-patent biopharmaceutical drugs

Brand name	Generic name	Indication	Marketer	Year of US patent expiration
Cerezyme	Imiglucerase	Gaucher disease	Genzyme	2001
Ceredase	Alglucerase	Gaucher disease	Genzyme	2001
Rebetron combination therapy	Ribavirin and interferon α-2b	Hepatitis C	Schering-Plough	2001
Intron A	Interferon α-2b	Leukemia, hepatitis B and C, melanoma, lymphoma	Schering-Plough	2002
Humulin	Human insulin	Diabetes	Eli Lilly	2002
Novolin	Human insulin	Diabetes	Novo Nordisk	2005
Avonex	Interferon β-1a	Multiple sclerosis	Biogen	2003
Humatrope	Somatropin	Growth hormone deficiency	Eli Lilly	2003
Nutropin/Nutropin AQ	Somatropin	Growth hormone deficiency	Genentech	2003
Epogen/Procrit	Erythropoetin α	Anemia	Amgen, Johnson & Johnson and Sankyo	2004
Geref	Sermorelin	Growth hormone deficiency	Serono	2004
Synagis	Palivizumab	Respiratory syncytial virus	Abbott Laboratories	2004
Activase	Alteplase	Myocardial infarction, stroke, pulmonary embolism	Genentech, Boehringer Ingelheim, Mitsubishi and Kyowa Hakko Kogyo	2005
Protropin	Somatrem	Growth hormone deficiency	Genentech	2005
Neupogen	Filgrastim	Neutropenia	Amgen and Roche	2006

Source: DataMonitor (http://www.datamonitor.com/) and ABN Amro (http://www.abnamro.com/)

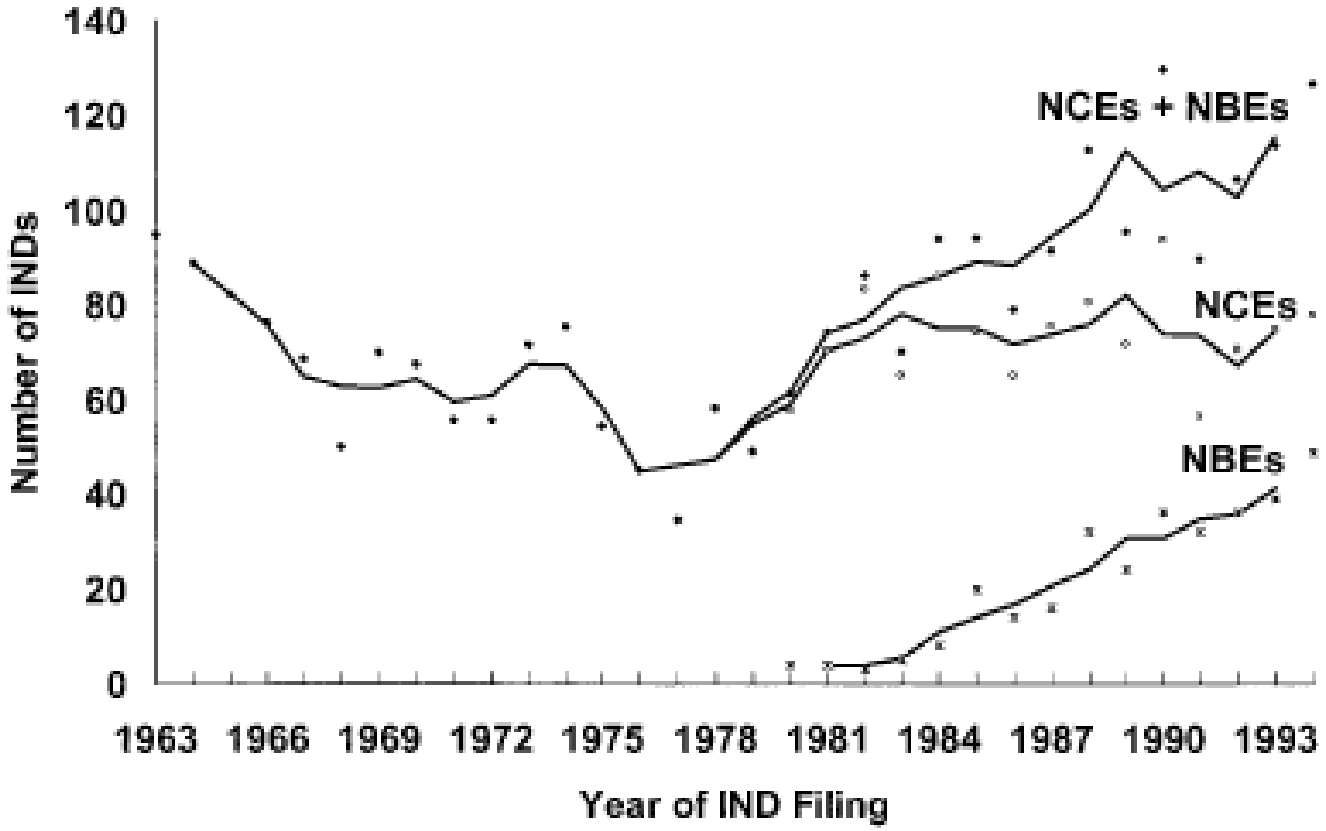
Indian biogeneric firms

Table 1 Select Indian biogeneric firms

Firm	Products on market	Products in development
Shantha Biotech (Hyderabad)	Hepatitis B vaccine; interferon (IFN)-α	Insulin; granulocyte macrophage colony stimulating factor (GM-CSF); granulocyte-colony stimulating factor (G-CSF); streptokinase; tissue plasminogen-activating factor (tPA); erythropoietin (EPO); human growth hormone (hGH)
Bharat Biotech (Hyderabad)	Hepatitis B vaccine; streptokinase; lysostaphin	Vascular endothelial growth factor (VEGF)
Dr. Reddy's Labs (Hyderabad)	G-CSF	Erythropoietin (EPO); IFN-β; hGH; tPA; IFN-γ; 5 other undisclosed recombinant biologics
Ranbaxy (New Delhi)	None	Signed agreements to in-license IFN-α-2b, G-CSF and EPO
Wockhardt (Mumbai)	EPO; hepatitis B vaccine; insulin	IFN-α-2b

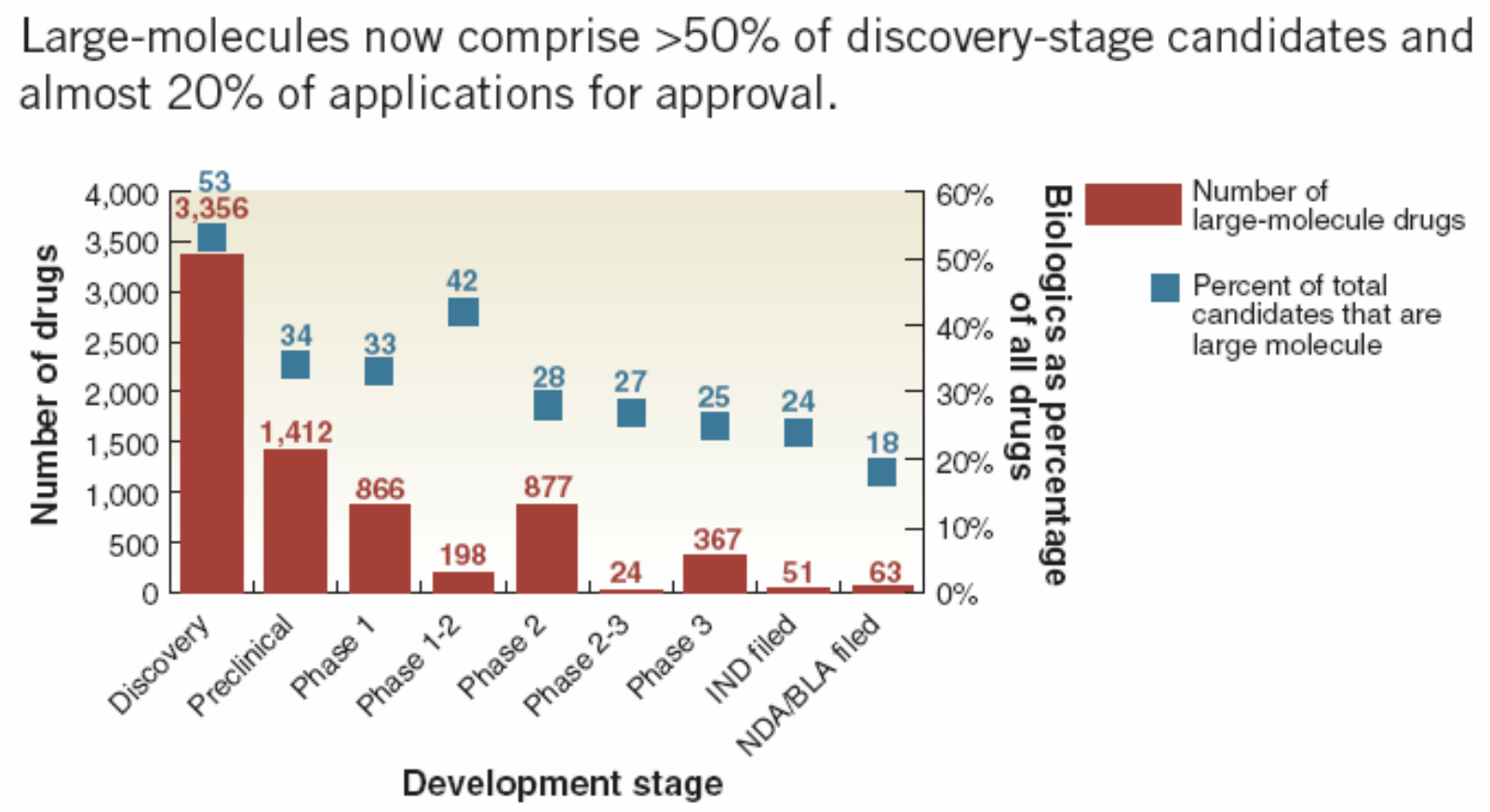
Source: BioCentury.

The expansion of clinical development of biotechnology drugs has driven the increase in the total number of molecules investigated in the United States during the 1980s and 1990s



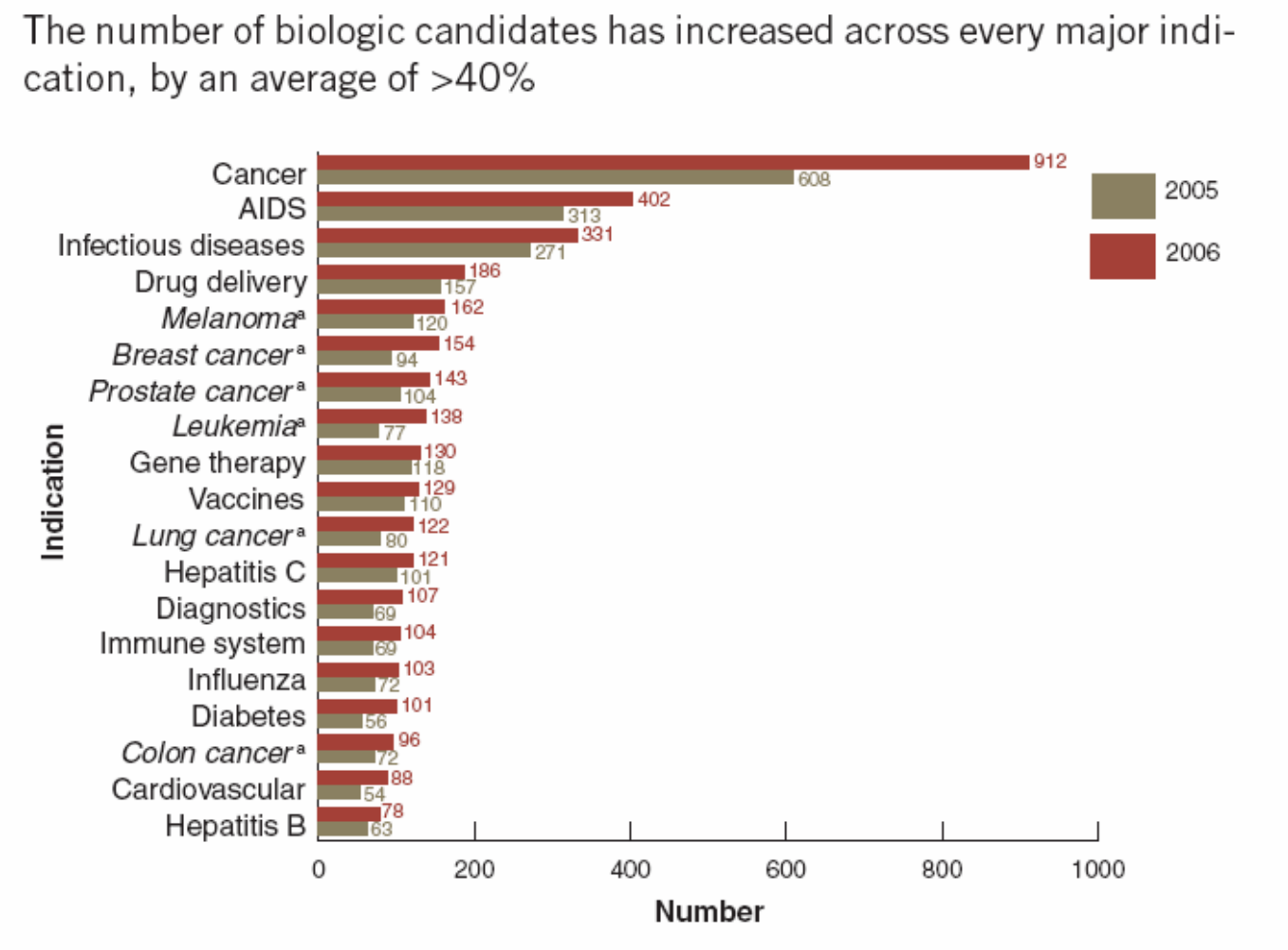
Source: Di Masi, 2001

Biotech drug candidates by phase



Source: Nature Biotechnology, Dec. 2006

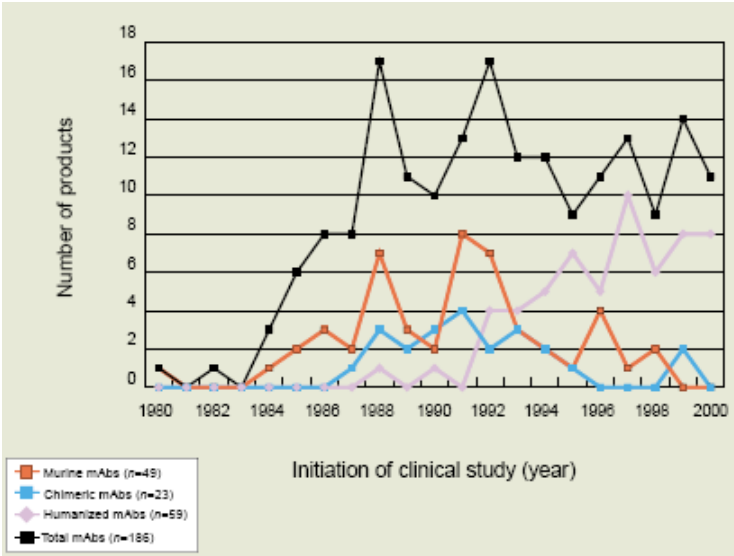
Biopharmaceuticals by therapeutic category.



Source: Nature Biotechnology, Dec. 2006

Second generation (engineered) Biopharmaceuticals (1)

Product name and company	Indication
Altered amino acid sequence	
Humalog & Liprolog (Insulin analogue; Eli Lilly)	Diabetes
NovoRapid/Novolog (Insulin analogue, Novo nordisk)	Diabetes
Lantus/Optisulin (Insulin analogue; Aventis)	Diabetes
Retavase (tPA analogue; Boehringer-Manheim/ Centocor), also Ecokinase (Galenus Mannheim) and Rapilysin (Boheringer-Manheim)	Thrombolytic agent
TNKase (tPA analogue; Genentech/Schering plough)	Thrombolytic agent
Simulect (Engineered Mab; Novartis)	Prevention of acute kidney transplant rejection
Remicade (Engineered Mab; Centocor)	Treatment of Crohn's disease
Mabthera (Engineered Mab; Hoffmann-La Roche)	Treatment of non-Hodgkin's lymphoma
Rituxan (Engineered Mab; Genentech and IDEC)	Treatment of non-Hodgkin's lymphoma
ReoPro (Engineered Mab; Centocor)	Prevention of blood clots
Zenapax (Engineered Mab; Roche)	Prevention of acute kidney transplant rejection
Synagis (Engineered Mab; Abbott)	Prophylaxis of lower respiratory disease caused by respiratory syncytial virus
Herceptin (Engineered Mab; Roche)	Treatment of some forms of breast cancer
Xolair (Engineered Mab; Genentech and Novartis)	Treatment of moderate to severe persistent asthma
Mabcampath/Campath (Engineered Mab; ILEX, Millennium and Berlex)	Chronic lymphocytic leukaemia
Mylotarg (Engineered Mab; Wyeth)	Acute myeloid leukaemia
Infergen (IFN analogue; Amgen)	Treatment of chronic hepatitis C
ReFacto (Blood factor VIII analogue; Genetics Institute)	Haemophilia A
Ontak (Fusion product; Seragen/Ligand)	Treatment of cutaneous T cell lymphoma
Enbrel (Fusion product; Immunex)	Rheumatoid arthritis
Amevive (Fusion product; Biogen)	Moderate to severe chronic plaque psoriasis



Altered carbohydrate component	
Cerezyme (Glucocerebrosidase enzyme; Genzyme)	Gaucher's disease
Nespo/Aranesp (EPO; Amgen)	Anemia
Covalently attached polyethylene glycol	
Pegasys (IFN; Hoffman La Roche)	Hepatitis C
Viraferon Peg/PegIntron (IFN; Schering plough)	Hepatitis C
Somavert (hGH analogue; Pharmacia)	Acromegaly
Neulasta (G-CSF; Amgen)	Neutropenia

Second generation (engineered) Biopharmaceuticals (2)

Rationale:

1) The reduction/elimination of product immunogenicity
   (es. Chimaeric and Humanized antibody-based products);

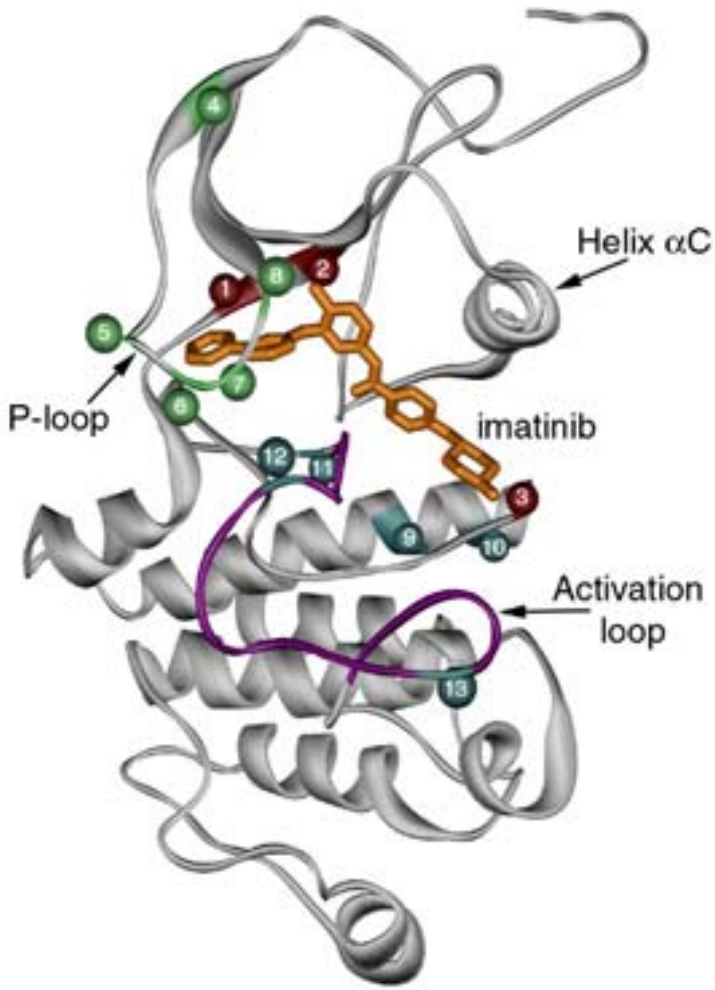
2) The generation of products with altered
   pharmacokinetic profiles
   (es. Fast- and slow-acting insulins);

3) The alteration of biological half life
   (es. Engineered tissue plasmogen activator-based products);

4) The generation of novel (hybrid) proteins
   (es. Amevive and Enbrel).

Is Gleevec a biopharmaceutical?

- BIO includes Gleevec™ (imatinib mesylate) of Novartis in the list of biopharmaceutical drugs but:
  - It is a small molecule
  - It is not bioprocessed
  - Related patents are not classified as biotech



The R&D cost of Biopharmaceuticals

The Tufts Center for the Study of Drug Development investigated clinical study data for 12 new biopharmaceutical products as compared to the results of published clinical study data for new molecular entities (NMEs) and new active substances (NASs).
The development of the biopharmaceuticals involved significantly fewer studies per application compared with the studies of NASs and also fewer subjects per application compared with the studies of either NMEs or NASs.

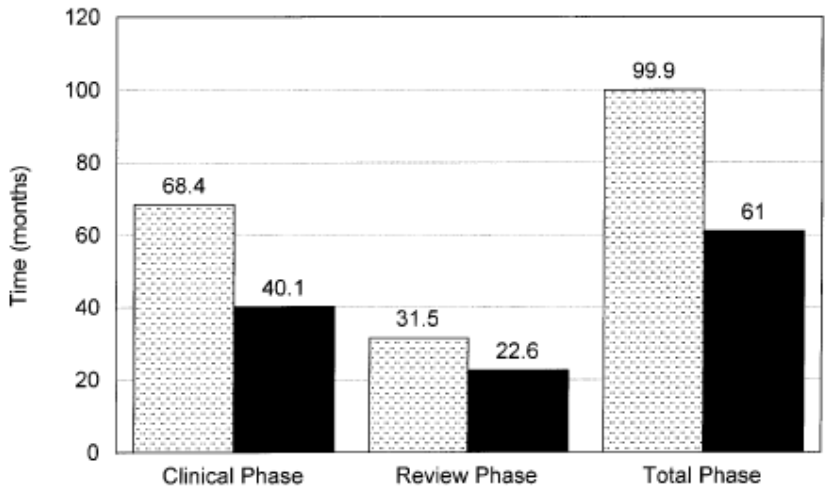


FIGURE 1. New biologic entities and new chemical entities approved 1980–1994: A comparison of development phase lengths. The clinical phase, review phase, and total phase lengths of drug development are as defined in "Methods." Shown are the means of the three phases for the new biologic entities (solid bars, n = 29) and the new chemical entities (stippled bars, n = 303) approved in the United States during 1980–1994.

A possible reason for this finding is that many of the biopharmaceuticals included in the analysis were treatments for diseases that affect a potentially small number of subjects, that is, **rare, serious, or life-threatening diseases.**

Some basic features of innovation in biopharmaceuticals (1)

- The DBFs are not specialized in more risky R&D projects. In fact, more risky drug projects (i.e. drugs for which there is no or there are few existing remedies) are more likely to be undertaken by the larger pharmaceutical companies. This suggests that scale, market power, and the ability to mobilize large amounts of resources are key factors in enabling the firms to sustain such higher risks.
- Other things being equal, the projects originated by the DBFs are more likely to fail in the earlier clinical stages. This suggests that the DBFs perform a good deal of exploration without incurring the higher costs of failing at later stages.

Some basic features of innovation in biopharmaceuticals (2)

We used a set of multiple indicators to describe and assess every indication in terms of outcome, presence of organ damage or complication, etiology, chronicity, diffusion and the eventual existence of a pharmacological therapy.

In order to quantify the severity of a disease, we have considered three aspects in absence of therapy: the outcome, distinguishing diseases that are life threatening, the presence of organ damage, and the possibility of developing complications. Moreover we considered information about the etiology of the disease (unknown or monofactorial, versus multifactorial), its chronicity , the existence of pharmacological therapies, and its diffusion.

Some basic features of innovation in biopharmaceuticals (3)

Classes of Risk Originators	R1	R2	R3	Total
NBFs	184	394	131	709
%	25,95	55,57	18,48	100
Large Pharmas	223	703	348	1274
%	17,5	55,18	27,32	100
Universities	15	57	23	95
%	15,79	60	24,21	100
Total	422	1154	502	2078
%	36,57	229,88	24,16	100

Some basic features of innovation in biopharmaceuticals (4)

		Low	Medium	High
NBFs	*Risk*	*25,95*	*55,57*	*18,48*
	Market Size	43,23	43,75	13,02
	Novelty	37,10	52,93	9,97
Large Pharma	*Risk*	*17,50*	*55,18*	*27,32*
	Market Size	37,47	45,27	17,26
	Novelty	42,05	50,71	7,24

Success: Biotech versus Pharma
Probit Estimates.
Dependent Variable = 1 if Success.

Parameter	Estimate	Std. Error
Constant	-2.67	1.07
Morbidity	0.02	0.10
Common	-0.21	0.16
Causes	0.46**	0.11
Remedies	0.33**	0.14
Chronic	-0.50**	0.20
Biotech Firm Dum	0.12	0.13
Obs (Positive Obs)	910 (78)	
Log Lik	-251.1	

Bottom Line: Biotechs not markedly better in this sample

Success: Biotech (licensed and in-house) versus Pharma
Probit Estimates.
Dependent Variable = 1 if Success.

Parameter	Estimate	Std. Error
Constant	-2.80**	1.11
Morbidity	0.02	0.10
Common	0.17	0.17
Causes	0.49**	0.12
Remedies	0.32**	0.15
Chronic	-0.50**	0.21
Biotech * License	1.47**	0.22
Biotech*(1-License)	-0.14	0.14

Obs (Positive Obs)	910 (78)
Log Likelihood	-223.1

Bottom Line: No evidence of "lemons problem"

Findings and tentative conclusions

1. Licensed compounds have substantially higher probability of success.

2. Biotech firms have greater probability (likely!!) to originate successful drugs.

3. Biotechs have a higher share of failures early.

4. Pharma have an edge in development which partially compensates for apparent lower probability of originating successful drugs.

Possible Implications

1. No "lemons" problem in market for technology
2. Biotechs have higher development costs for later clinical (e.g., higher cost of capital; poor links with hospitals and physicians) – but should also imply lower probability of early failure.
3. Biotechs have lower false positives in early clinicals.
4. Pharma have lower false negatives in early clinicals.
5. Biotechs have a superior distribution of projects from which to draw — (but should imply lower probability of early failure)

The price of biopharmaceuticals

Table 1. Molecular Medications

Indication/Medication	Year Approved*	B/D	Manufacturer	Cost per 30 Days $	U.S. Sales 2004 (million $)
Chronic hepatitis C					
Pegylated interferon alfa-2a (Pegasys)	2002	B	Hoffman	1,445	420
Pegylated interferon alfa-2b (PEG-Intron)	2001	B	Schering	1,308	563
Rheumatoid arthritis					
Etanercept (Enbrel)	1998	B	Amgen	1,280	1,500
Adalimumab (Humira)	2002	B	Abbott	1,217	460
Cancer					
Gefitinib (Iressa)	2003	D	AstraZeneca	1,806	389
Imatinib (Gleevec)	2001	D	Novartis	2,440	368
Erlotinib (Tarceva)	2004	D	OSI	1,899	13†
Thalidomide (Thalidomid)	1998	D	Celgene	2,268	309
Multiple sclerosis					
Glatiramer (Copaxone)	1996	D	Teva	1,300	605
Interferon beta-1a (Rebif)	2002	B	Serono	1,391	230
Interferon beta-1b (Betaseron)	1993	B	Serono	1,300	380

Note: Sales figures based on of Schering, Hoffman, Serono, Teva, Selgene, Novartis, OSI, and AstraZeneca 2004 annual reports. Drug prices based on EPO-CRATES.com retail prices.

* Year approved by the Food and Drug Administration (FDA).

† Approved November 2004.

B = biological; D = drug.

Source: Gillick (2006)

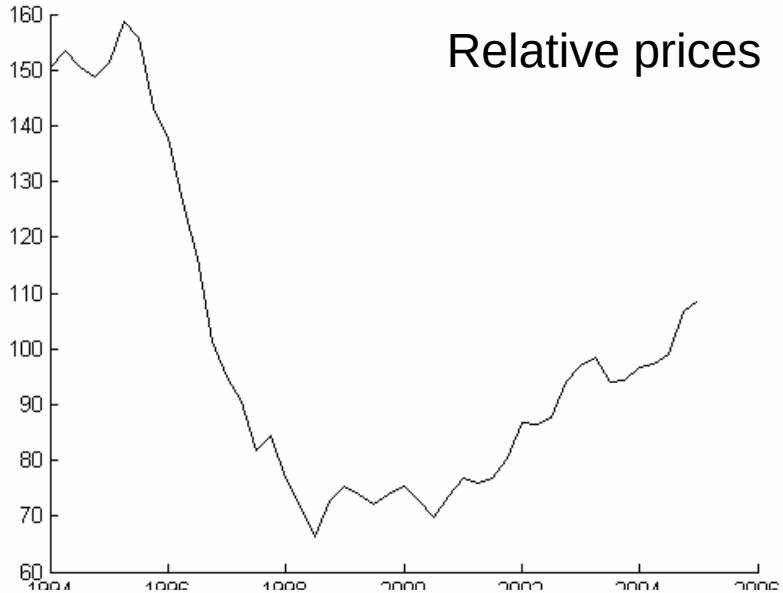
Top ten biotech drugs by global sales

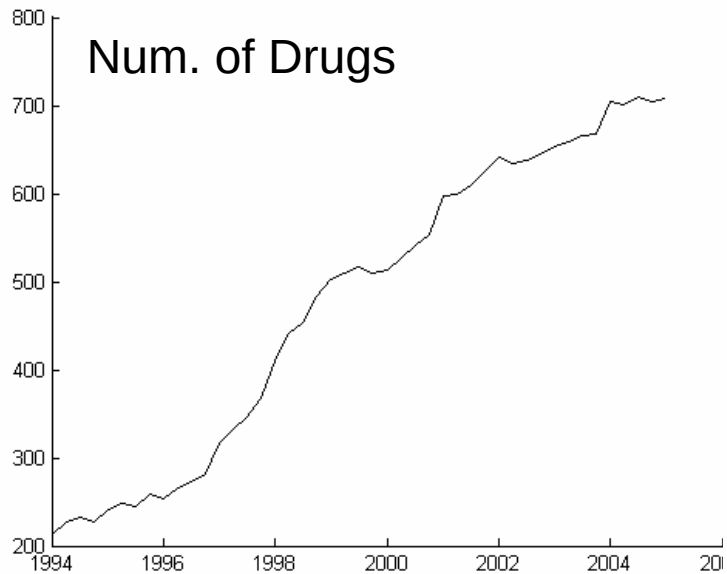
Product/company	Type	2005 sales ($ millions)	1H2006 Sales ($ millions)
Enbrel (etanercept)/Amgen/ Wyeth	Recombinant fusion protein; soluble TNF receptor linked to IgG1	3,657	2,087
Remicade (infliximab)/ Centocor	Chimeric mAb; anti-TNF-alpha	3,477	2,042
Aranesp (darbepoetin alfa)/ Amgen	Recombinant erythropoietin with two additional N-glycosylation sites	3,273	1,948
Rituxan (rituximab)/ Biogen-Idec/Genentech	Chimeric mAb; anti-CD20	3,154	1,917
Procrit (erythropoietin)/Amgen	Recombinant erythropoietin	3,324	1,594
Herceptin (trastuzumab)/ Genentech	Humanized mAb; anti-HER-2	1,629	1,480
Neulasta (PEG-filgrastim)/ Amgen/Dompec Biotech	Recombinant methionyl human granulocyte colony stimulating factor (Filgrastim) conjugated to monomethoxypolyethylene glycol	2,288	1,309
Epogen (erythropoietin)/Amgen	Recombinant erythropoietin	2,455	1,217
Avastin (bevacizumab)/ Genentech	Humanized mAb; anti-vascular endothelial growth factor	1,264	1,134
Epogin/NeoRecormon (Roche)	Recombinant erythropoietin	1,710	898

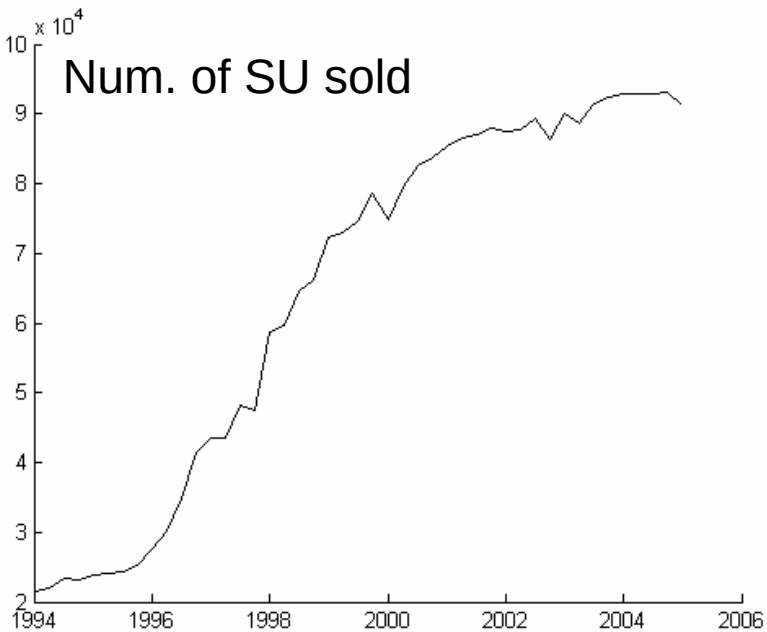
mAb, monoclonal antibody; TNF, tumor necrosis factor. Source: Signals, Recombinant Capital

Source: Nature Biotechnology, Dec. 2006

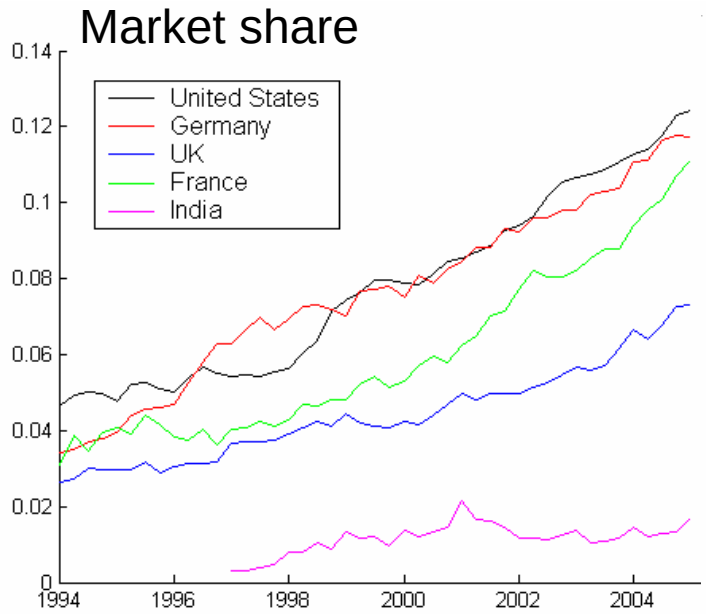
The US biopharmaceutical market

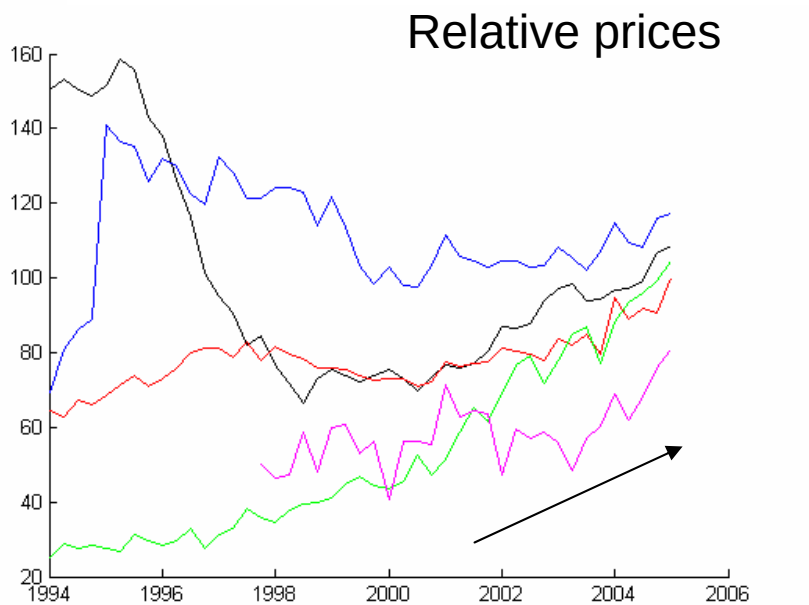


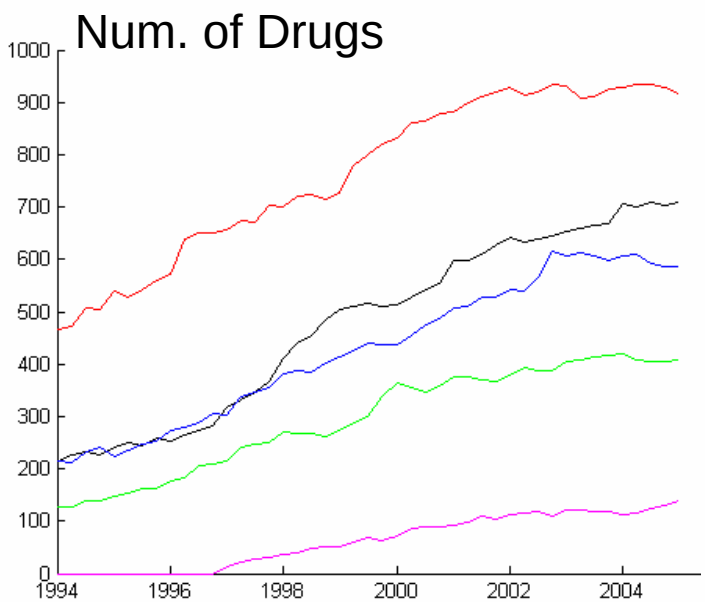


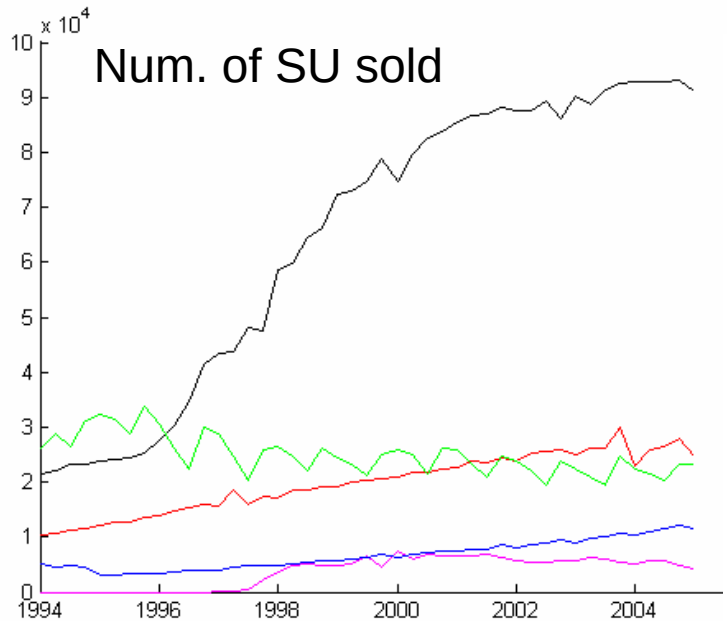


International comparison









Biopharmaceutical products

Country	Hospital	Pharmacy	Grand Total
Germany	587	1020	1607
USA	554	600	1154
Italy	474	451	925
Austria	458	455	913
UK	505	399	904
Japan	436	439	875
Netherlands	298	388	686
Finland	305	310	615
Spain	323	272	595
France	353	228	581
Poland	238	232	470
Belgium	265	204	469
Czech	221	237	458
China	452	NA	452
Sweden	NA	NA	450
Canada	207	218	425
Hungary	234	186	420
Denmark	NA	NA	353
Ireland	NA	301	301
Slovak	121	177	298
Greece	NA	286	286
Lithuania	77	119	196
India	NA	182	182
Luxembourg	NA	182	182
Slovenia	NA	NA	168
Portugal	NA	112	112
Estonia	NA	102	102
Latvia	NA	99	99

Price at launch

Walsh definition

	Mean	Median
Canada	10.4155	8.2966
USA	13.5215	1.5102
Cina	2.8814	2.883
France	2.8867	2.5373
Germany	20.7661	1.8965
India	6.6436	6.0564
Italy	1.6882	1.2806
Japan	38.6961	35.6478
Spain	1.7218	1.6822
UK	27.5541	27.4408

BIO Definition

	Mean	Median
Canada	7.4858	7.4845
USA	7.9559	2.5203
Cina	1.4964	1.4964
France	1.7173	1.7179
Germany	14.4402	14.3841
India	2.3304	2.2989
Italy	1.4491	1.4171
Japan	1.7986	1.7986
Spain	1.7208	1.7209
UK	2.5219	2.5219

Conclusions

- The incresing number of new biologicals, price and sales trends in a regime of production and regulatory constraints, raise serious concerns as far as future access, diffusion and sustainability of (bio)pharmaceutical innovation.

- Need for a common definition of biopharmaceuticals;

- In order to guarantee the future sustainability of biopharmaceuticals:
  - Favour off patent competition (biogenerics, or biological follow-ons), within the jurisdiction of the FDA, EMEA and other national authorities;
  - Patent reform so as to foster dynamic competition in the field of molecular medicine;
  - Establish standards for approving biogenerics using an expedited pathway, similar to the review process for generic versions of conventional drugs (biogenerics have already appeared in India, China, Latin America, and the Middle East)