Biofarmacevtiki

Glavni bioprodukti v letih od 2005-2007

product	annual production (kton)	annual market size (B$)
bioethanol	>50,000	>10
amino acids (except chemically produced D,L-methionine)	>3000	3.7 (41% L-glutamic acid, 41% L-lysine.HCl, 8% L-threonine, 10% others)
citric acid	1,800	1.6
lactic acid	250	>0.5
ascorbic acid (vitamin C)	107	0.5
anti-infective antibiotics	>100	55 (160 products: 36% β-lactams, 19% antivirals, 12% quinolones, 11% macrolides, 22% other)
industrial enzymes	>100	2.3 (34% detergents, 27% foods, feeds 16%, textiles 10%, other 13%)
gluconic acid	60	0.13
xanthan	30	0.4
pharmacological agents	<10	>50 (statins, cyclosporines, etc.)
riboflavin (vitamin B2)	5	0.13
biopharmaceuticals	<1	63 (200 products: 21% EPO, 11% MAbs, 10% interferon, 9% human insulin, 50% other)

Vir: **Key Green Engineering Research Areas for Sustainable Manufacturing: A Perspective from Pharmaceutical and Fine Chemicals Manufacturers** *Org. Process Res. Dev.* 2011, 15, 900–911

Concepción Jiménez-González,[*,†] Peter Poechlauer,[‡] Quirinus B. Broxterman,[§] Bing-Shiou Yang,[⊥] David am Ende,[∥] James Baird,[▼] Carl Bertsch,[□] Robert E. Hannah,[■] Phil Dell'Orco,[○] Henk Noorman,[●] Sandy Yee,[△] Raf Reintjens,[§] Andrew Wells,[▲] Viviane Massonneau,[▽] and Julie Manley[▼]

Ključne prioritete za trajnostno proizvodnjo

Key green engineering research areas: results of the brainstorming and prioritization exercises

Rank	Main Key Areas	Sub-areas/aspects	Votes
1	Continuous Processing	Primary, Secondary, Semi-continuous, etc.	12
2	Bioprocesses	Biotechnology, Fermentations, Biocatalysis, GMOs,	11
3	Separation and Reaction Technologies	Membranes, crystallizations, etc.	11
4	Solvent Selection, Recycle and Optimization	Property modeling, volume optimization, recycling technologies, in process recycle, regulatory aspects etc.	10
5	Process Intensification	Technology, process, hybrid systems, etc	9
6	Integration of Life Cycle Assessment (LCA)	Life cycle thinking, Total Cost Assessment, carbon / eco-footprinting, Social LCA, streamlined tools	4
7	Integration of Chemistry and Engineering	Business strategy, links with education, etc.	4
8	Scale up aspects	Mass and energy transfer, Kinetics, and others	3
9	Process Energy Intensity	Baseline for pharmaceuticals, estimation, energy optimization	1
10	Mass and Energy Integration	Process integration, Process Synthesis, Combined Heat and Power, etc	0

Vir:

Key Green Engineering Research Areas for Sustainable Manufacturing: A Perspective from Pharmaceutical and Fine Chemicals Manufacturers

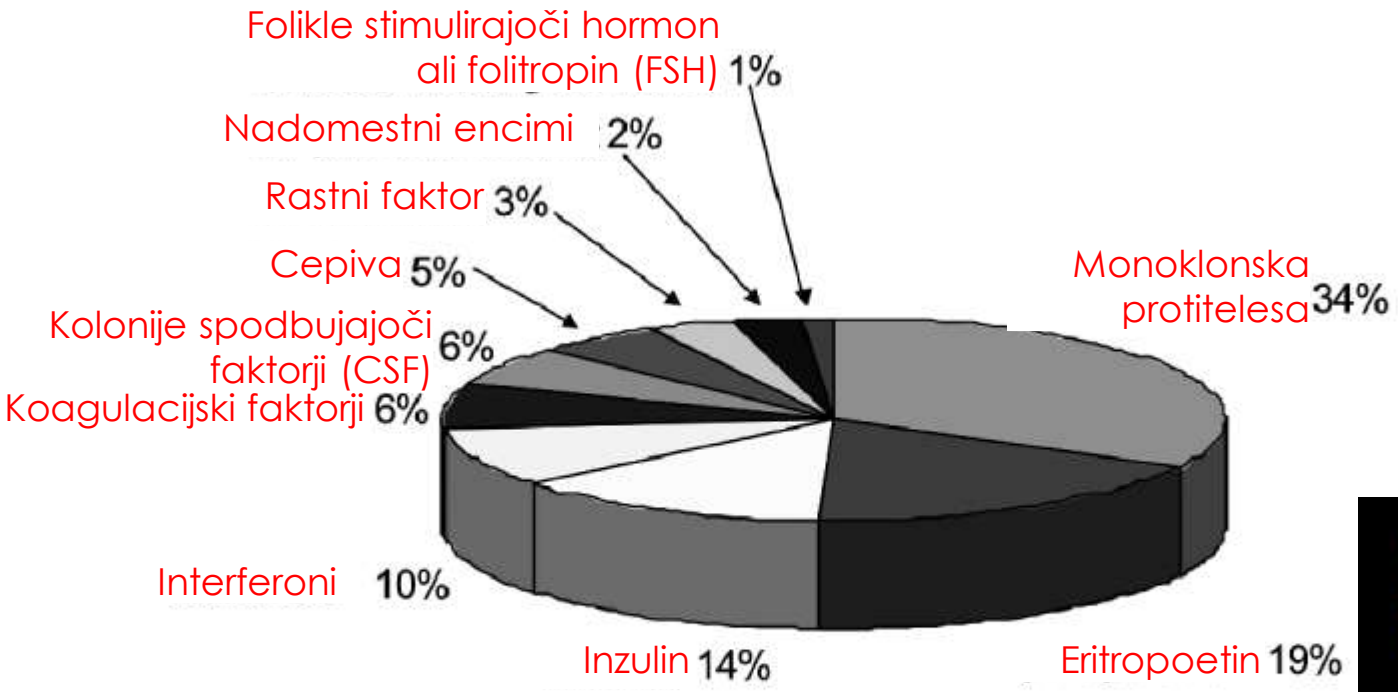
Concepción Jiménez-González,*,† Peter Poechlauer,‡ Quirinus B. Broxterman,§ Bing-Shiou Yang,⊥ David am Ende,∥ James Baird,¶ Carl Bertsch,□ Robert E. Hannah,■ Phil Dell'Orco,○ Henk Noorman,● Sandy Yee,△ Raf Reintjens,§ Andrew Wells,▲ Viviane Massonneau,▽ and Julie Manley▼

†GlaxoSmithKline, Sustainability and Environment, 5 Moore Drive, Research Triangle Park, North Carolina, United States
‡DSM Pharmaceutical Products, St.-Peter -Strasse 25, 4021 Linz, Austria
§DSM Innovative Synthesis B.V., P.O. Box 18, 6160 MD Geleen, The Netherlands
⊥Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877-0368, United States
∥Pfizer Inc., Chemical Research and Development, Pfizer, Groton, Connecticut 06340, United States
¶AstraZeneca, Essential Safety, Health and Environment, Alderley Park, Macclesfield, U.K.
□Eli Lilly and Co., Chemical Process Research and Development, Lilly Technology Center, Indianapolis, Indiana, United States
■GlaxoSmithKline, Sustainability and Environment, 1 Franklin Plaza, Philadelphia, Pennsylvania, United States
○GlaxoSmithKline, Research and Development, Upper Merion, Pennsylvania, United States
●DSM Biotechnology Center PO Box 425, 2600 AK Delft, The Netherlands
△Johnson & Johnson, EHS2 Compliance and Environmental Affairs, Global Pharma, 200 Tournament Drive, Horsham, Pennsylvania 19044, United States
▲AstraZeneca, Pharmaceutical Development, Bakewell Road, Loughborough, U.K.
▽Merck MSD Manufacturing, Z.I de Blavozy 43700 Saint Germain Laprade, France
▼ACS Green Chemistry Institute, 1155 Sixteenth Street, NW, Washington, DC 20036, United States

Org. Process Res. Dev. 2011, 15, 900–911

Deleži biofarmacevtikov na tržišču

proteinski terapevtiki leta 2006



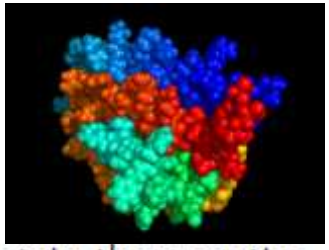


Figure 1.1 Biopharmaceuticals market share in 2006. Approximately 160 protein therapeutics have gained approval in the USA and EU. Data from La Merie Business Intelligence (www.lamerie.com).

Biološka zdravila

Biološka zdravila za zdravljenje revmatoidnega artritisa

Mesto delovanja	Zdravilo
Zaviralci TNF-α	etanercept, infliksimab, adalimumab, golimumab
Zaviralci receptorja IL-1	anakinra
Zaviralci receptorja IL-6	tocilizumab
Delovanje na B-celice	rituksimab

Biološka zdravila zavirajo imunske procese in tvorbo določenih posrednikov imunskega vnetja, zato jih imenujemo tudi selektivna imunomodulirajoča zdravila. Imunski sistem, predvsem pri bolnikih z revmatoidnim artritisom, tvori namreč preveč določenih beljakovin, kot so tumorje nekrotizirajoči faktorji alfa (skrajšano TNF-alfa) in interlevkina-1 in -6 (skrajšano IL-1, IL-6) ter še nekatere druge, ki so tudi pomembni posredniki sklepnega vnetja.

Zdravila anti-TNF-alfa vplivajo na molekule TNF-alfa tako, da se te ne morejo več vključevati v imunska in vnetna dogajanja. Zdravilo rituksimab zmanjšuje število vseh tistih belih krvničk B, ki imajo v celični membrani antigenom CD20. Te celice so sicer neposredno udeležene v vnetju sinovijske ovojnice sklepa. Zdravilo tocilizumab pa je monoklonsko protitelo usmerjeno proti receptorju interlevkina 6 (IL-6), ki je eden izmed ključnih citokinov udeleženih v vnetju pri RA.

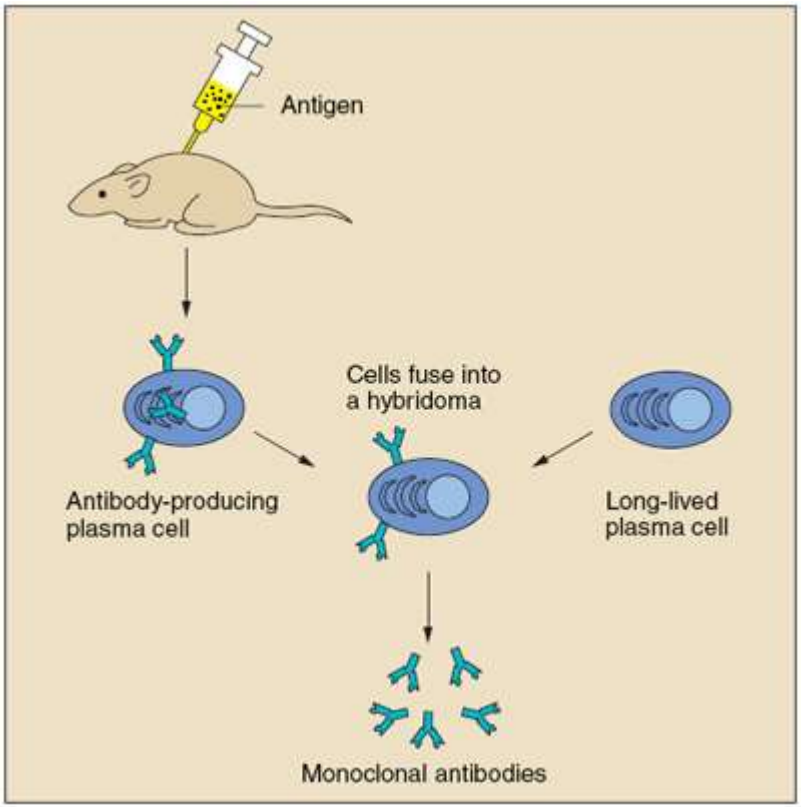
Najbolj prodajana biološka zdravila v letu 2012 (vir: *Genetic Engineering News*)

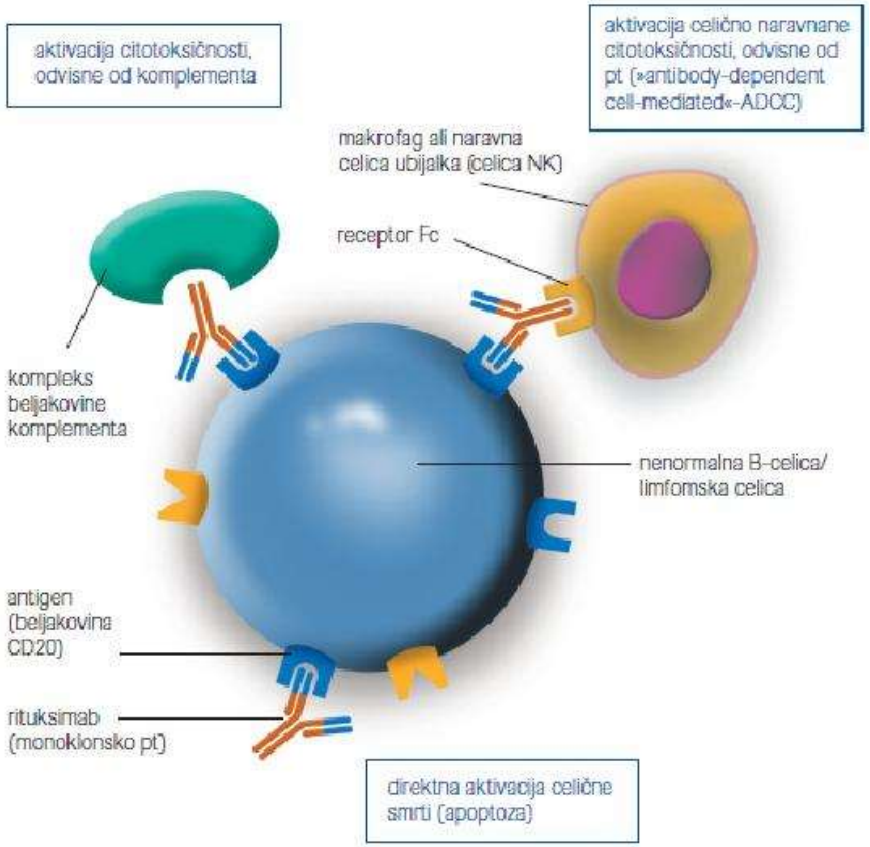
Uvrsti-tev	Biološko zdravilo	Ekspresijski sistem	Podjetje	Svetovna prodaja leta 2012 v milijonih $	Odobrene indikacije za uporabo
1	Humira (adalimumab = zaviralec TNF-alfa)	CHO (ovarijske celice kitajskega hrčka =Chinese hamster ovary cell)	AbbVie	9,265	Moderate to severe rheumatoid arthritis, moderate to severe chronic plaque psoriasis, moderate to severe Crohn's disease; moderate to severe ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, moderate to severe polyarticular juvenile idiopathic arthritis
2	Remicade (infliximab = zaviralec TNF-alfa)	Murine Myeloma (mielomske celice glodavcev)	Johnson & Johnson and Merck & Co.	8,215	Moderately to severely active rheumatoid arthritis in adults, in combination with methotrexate; Crohn's Disease in children 6 years and older, and adults who have not responded well to other medicines; rheumatoid arthritis; ankylosing spondylitis; psoriatic arthritis; chronic, severe, extensive, and/or disabling plaque psoriasis in adults; moderately to severely active ulcerative colitis in children 6 years and older and adults that have not responded well to other medicines
3	Enbrel (etanercept = zaviralec TNF-alfa)	CHO	Amgen and Pfizer	7,963	Moderate to severe plaque psoriasis, psoriatic arthritis, and moderate to severe rheumatoid arthritis

Najbolj prodajana ~~biološka zdravila~~ v letu 2012 (vir: *Genetic Engineering News*)

Uvrsti-tev	Biološko zdravilo	Ekspresijski sistem	Podjetje	Svetovna prodaja leta 2012 v milijonih $	Odobrene indikacije za uporabo
4	Rituxin (rituximab, MabThera = zaviralec CD20)	CHO	Roche and Biogen Idec	7,285	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis
5	Lantus (insulin glargine)	*E.coli*	Sanofi	6,648	Once daily treatment for diabetes
6	Herceptin (trastuzumab = zaviralec HER-2)	CHO	Roche	6,397	HER2-positive breast cancer and HER2-positive metastatic gastric cancer
7	Avastin (bevacizumab =zaviralec angiogeneze)	CHO	Roche	6,260	Metastatic colorectal cancer (colon cancer), non–small cell lung cancer, glioblastoma & metastatic kidney
8	Neulasta (pegfilgrastim = granulocitne kolonije stimulirajoči faktor)	*E.coli*	Amgen	4,092	Neutropenia caused by cancer chemotherapy

Monoklonska protitelesa





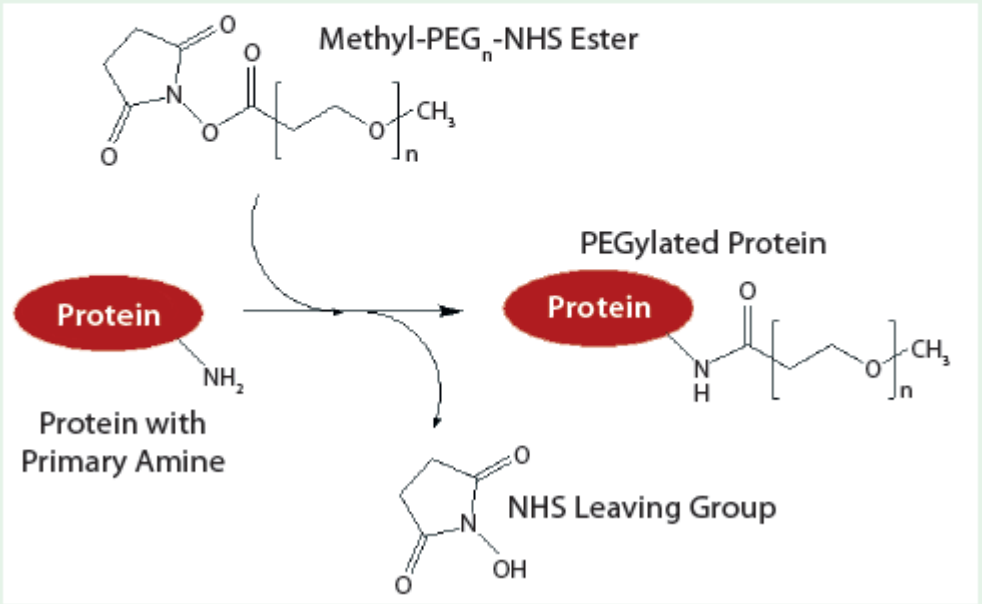
Monoklonska protitelesa se specifično vežejo na določeno tarčno beljakovino na površini limfomske celice (antigen) in nato sprožijo verižno reakcijo dogodkov, ki vodi v propad limfomskih celic.

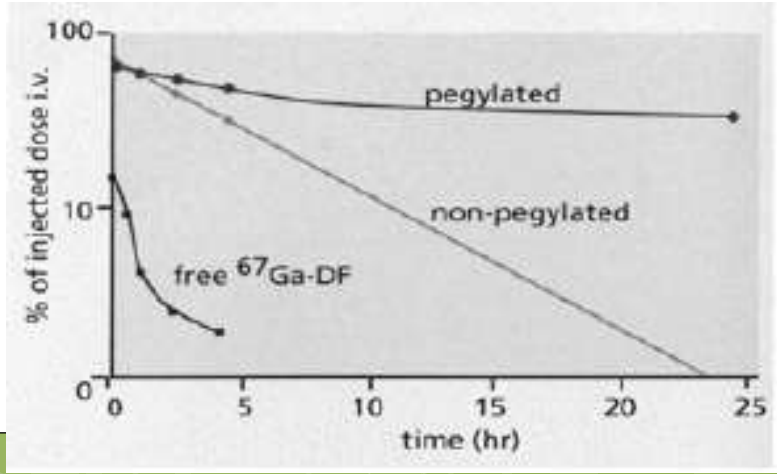
Pegilacija

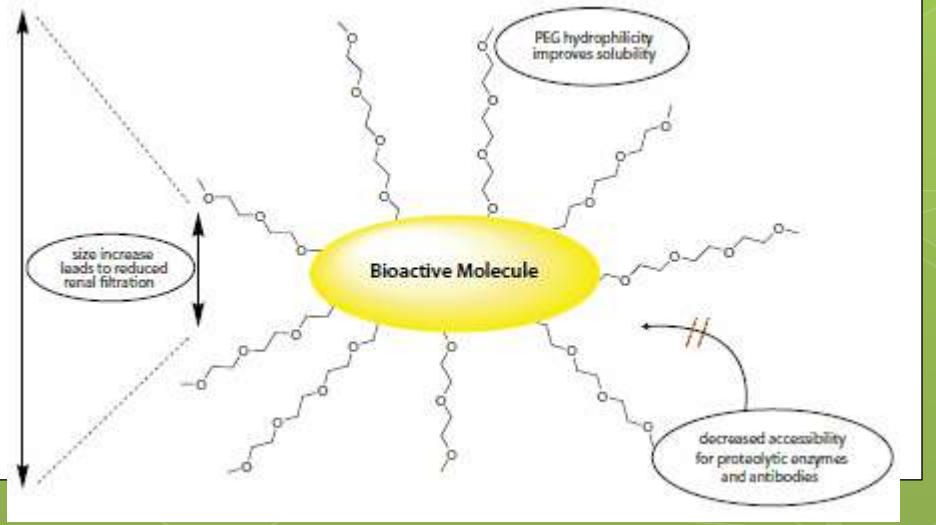
Izboljšana:

- Topnost v vodi
- Stabilnost v neugodnih okoljih (pH, topila, T...)
- Podaljšana razpolovna doba v telesu

Figure 1: Protein PEGylation with MS(PEG)n; proteins are many times larger than the PEGylation reagent and usually contain several amine groups, each of which could be labeled. (IAN N. ACWORTH, D.PHIL., DIRECTOR OF CUSTOMER AND APPLICATION SUPPORT FOR DIONEX PRODUCTS IN THE CHROMATOGRAPHY AND MASS SPECTROMETRY DIVISION AT THERMO FISHER SCIENTIFIC, CHELMSFORD, MA)







Pegilirani produkti na tržišču ZDA

Table 1: PEGylated products on the US biopharmaceutical market

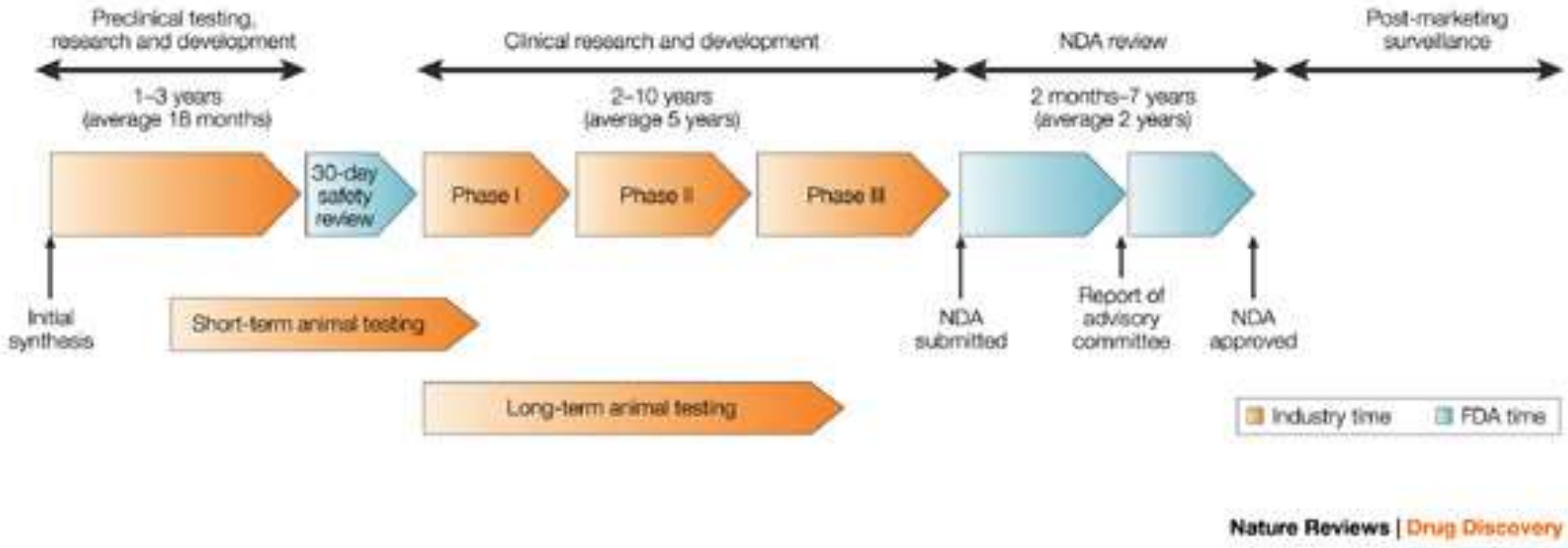
Product	Company	Approval Year	Indication
PEGinesatide (Omontys)	Affymax	2012	Anemia associated with chronic kidney disease
Pegloticase (Krystexxa)	Savient	2010	Gout
Certolizumab Pegol (Cimzia)	UCB Pharma	2008	Rheumatoid arthritis and Crohn's disease
Methoxy polyethylene glycol-epoetin beta (Mircera)	Roche	2007	Anemia associated with chronic kidney disease
Pegaptanib (Macugen)	Eyetech and Pfizer	2004	Neovascular age-related macular degeneration
PEG-human growth hormone mutein antagonist (Somavert)	Pfizer	2003	Acromegaly
Pegfilgrastim (Neulasta)	Amgen	2002	Severe cancer chemotherapy-induced neutropenia
PEGylated interferon alpha (PEGASYS)	Hoffmann-La Roche	2002	Chronic hepatitis C and hepatitis B
Peginterferon alpha-2b (Pegintron)	Schering-Plough and Enzon	2000	Chronic hepatitis C
Pegaspargase (Oncaspar)	Enzon	1994	Acute lymphoblastic leukemia in patients who are hypersensitive to the native unmodified form of L-asparaginase
PEG-adenosine deaminase (Adagen)	Enzon	1990	Severe combined immunodeficiency disease

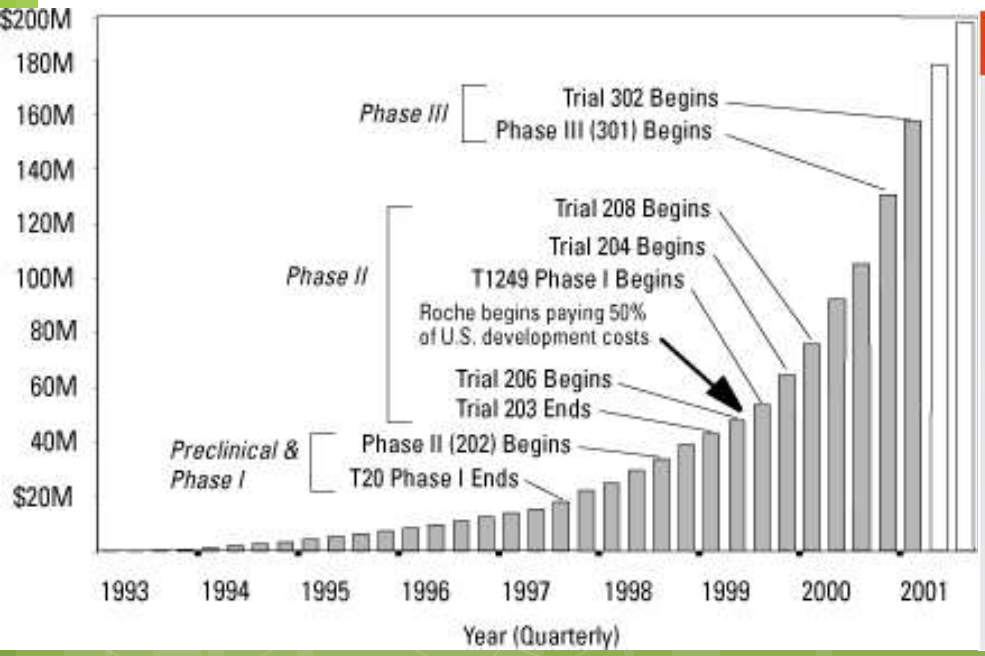
Table 2: Selected PEGylated products and technologies in the pipeline

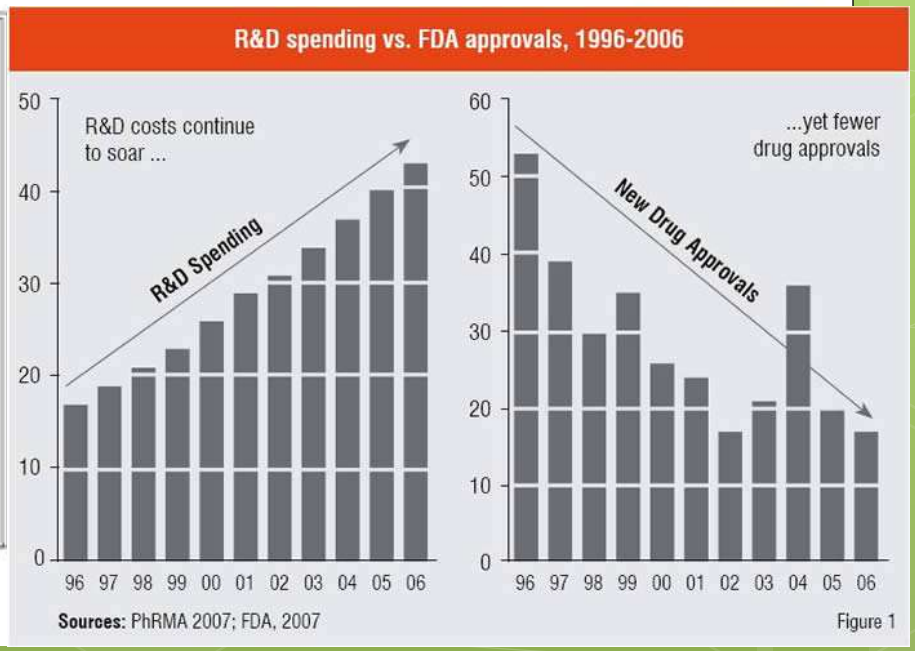
Company	Location (URL)	Technology	Service Provider?
Biomarin	Novato, CA (www.bmrn.com)	PEGylated recombinant phenylalanine ammonia lyase for the treatment of phenylketonuria; phase 2 clinical trial	No
PolyTherics	London, UK (www.polytherics.com)	PolyPEG comb-shaped structure with lower viscosity; development partners include Celtic Pharma Holdings (Factor VIIa, Factor VIII, and Factor IX), Nuron Biotech (recombinant human interferon beta-1b), and Spirogen (antibody drug conjugates).	No
Quanta Biodesign	Powell, OH (www.quantabiodesign.com)	dPEG agents with unique, specific molecular weights, providing homogeneous conjugates	No
Celares GmbH	Berlin, Germany (www.celares.com/Produkte/produkte.php?lang=en)	Branched PEG covers the molecule almost completely.	Yes
Enzon	Piscataway Township, NJ (http://enzon.com)	PEGylated conjugate of SN38 for treatment of metastatic breast cancer (phase 2), metastatic colorectal cancer (phase 2), pediatric solid tumors (phase 1), and solid tumors (phase 1).	No
Creative Biolabs	Shirley, NY (www.creative-biolabs.com/pegylation.htm)	N-terminal, thio-specific, and enzymatic PEGylation using transglutaminase	Yes
Creative PEGWorks	Winston Salem, NC (www.creativepegworks.com)	Reagents for PEGylation sites including amino, N-terminal, caroboxyl, thiol, hydroxyl, click, and surface PEGylation	Yes
NOF Corporation	Tokyo, Japan (www.peg-drug.com)	Reagents for multiple-arm PEG, bifunctional PEG, branched PEG, forked PEG, heterofunctional PEG, biocompatible PEG anchor, lysine branched PEG, and releasable PEG	No
Sigma Aldrich	St. Louis, MO (www.sigmaaldrich.com)	Monofunctional, homobifunctional, heterobifunctional, and monomethoxy endcapped PEG reagents	Yes
Prolong Pharmaceuticals	South Plainfield, NJ (www.prolongpharmaceuticals.com)	Sanguinate (a PEGylated oxygen transfer agent to delivery oxygen to anemic, diseased, and injured tissues); in clinical trials	No
Mountain View Pharmaceuticals	Menlo Park, CA (www.mvpharm.com)	PharmaPEG reagents are designed to reduce antigenicity and immunicity compared with standard PEG	No
Bolder Bio	Boulder, CO (www.bolderbio.com)	Site-specific protein PEGylation at cysteine residues; products in development target growth hormone deficiency, multiple sclerosis, anemia, neutropenia, hepatitis B and C, immunodeficiencies, and thrombocytopenia.	No

Regulatorne omejitve bioprocesov

- Glavni cilji bioprocesnih inženirjev:
  - Proizvodnja produkta dovolj visoke kvalitete za zadovoljitev zahtev regulatornih organov (FDA = Food and Drug Administration v ZDA)
  - Znižanje stroškov proizvodnje
- FDA odobritev **za produkt in proces skupaj**!
- Tipični proces pridobivanja odobritve FDA:
  - Odkritje + predklinični testi na živalih: cca 6,5 let
  - Klinični testi 1. faze (20 – 80 prostovoljcev): cca1 leto
  - Klinični testi 2. faze (100 – 300 pacientov): cca 2 leti
  - Klinični testi 3. faze (1000 – 3000 pacientov): cca 3 leta
  - Pregled rezultatov pred odobritvijo: cca 1,5 let
  - Skupaj povprečno15 let, cena: 400 milijonov $ (1996)
  - 10 % zdravil pridobi odobritev


Preclinical testing, research and development
1–3 years (average 18 months)
Clinical research and development
2–10 years (average 5 years)
NDA review
2 months–7 years (average 2 years)
Post-marketing surveillance
30-day safety review
Phase I
Phase II
Phase III
Initial synthesis
Short-term animal testing
Long-term animal testing
NDA submitted
Report of advisory committee
NDA approved
Industry time
FDA time
Nature Reviews | Drug Discovery


$200M
180M
160M
140M
120M
100M
80M
60M
40M
$20M
Phase III
Trial 302 Begins
Phase III (301) Begins
Phase II
Trial 208 Begins
Trial 204 Begins
T1249 Phase I Begins
Roche begins paying 50% of U.S. development costs
Trial 206 Begins
Trial 203 Ends
Preclinical & Phase I
Phase II (202) Begins
T20 Phase I Ends
1993
1994
1995
1996
1997
1998
1999
2000
2001
Year (Quarterly)


R&D spending vs. FDA approvals, 1996-2006
R&D costs continue to soar ...
R&D Spending
...yet fewer drug approvals
New Drug Approvals
96 97 98 99 00 01 02 03 04 05 06
Sources: PhRMA 2007; FDA, 2007
Figure 1

Regulatorne omejitve bioprocesov

- FDA odobritev **za produkt in proces skupaj**!
- Majhne spremembe v procesu lahko privedejo do tragičnih posledic.
- Sprememba procesa zahteva ponovne klinične teste.
- Zdravila na tržišču in uporabljena v kliničnih testih morajo biti proizvedena v skladu z dobro proizvodno prakso (GMP = good manufacturing practice)

GMP in GLP

- Dobra proizvodna praksa (GMP) se nanaša na:
  - uporabljeno proizvodno opremo in postopke (ne sme priti do kontaminacij produkta, določen tok snovi, osebja in zraka)
  - usposobljenost osebja v proizvodnji
  - nadzor vstopnih snovi (surovine, kulture)
  - ravnanje s produktom
  - vsi računalniški programi morajo biti validirani
- Off- line analize morajo biti narejene v skladu z dobro laboratorijsko prakso (GLP = good laboratory practice)
- Postopki so dokumentirani z SOP (standard operating procedures).

Validacija procesa

- Običajno zelo dolgotrajni in kompleksni postopki.
- „Validacija procesa je uveljavljanje dokumentiranega dokaza, ki daje visoko stopnjo zagotovitve, da bo specifični proces konsistentno proizvajal produkt, ki bo v skladu z njegovimi predhodno določenimi specifikacijami in karakteristikami kvalitete.“