BiopolyMed

the BIOTECHNOLOGY day

For a discussion of research and applications related to Biotechnology and its future prospects in the United Arab Emirates

Application of Biotechnology

PEGylation: Successful Technology to Develop the 2nd Generation of Therapeutic Biologics

United Arab Emirates University – Al Ain
Faculty of Information Technology Auditorium (Male)
Wednesday 27th, October 2010
10:00am

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BiopolyMed, Inc.,

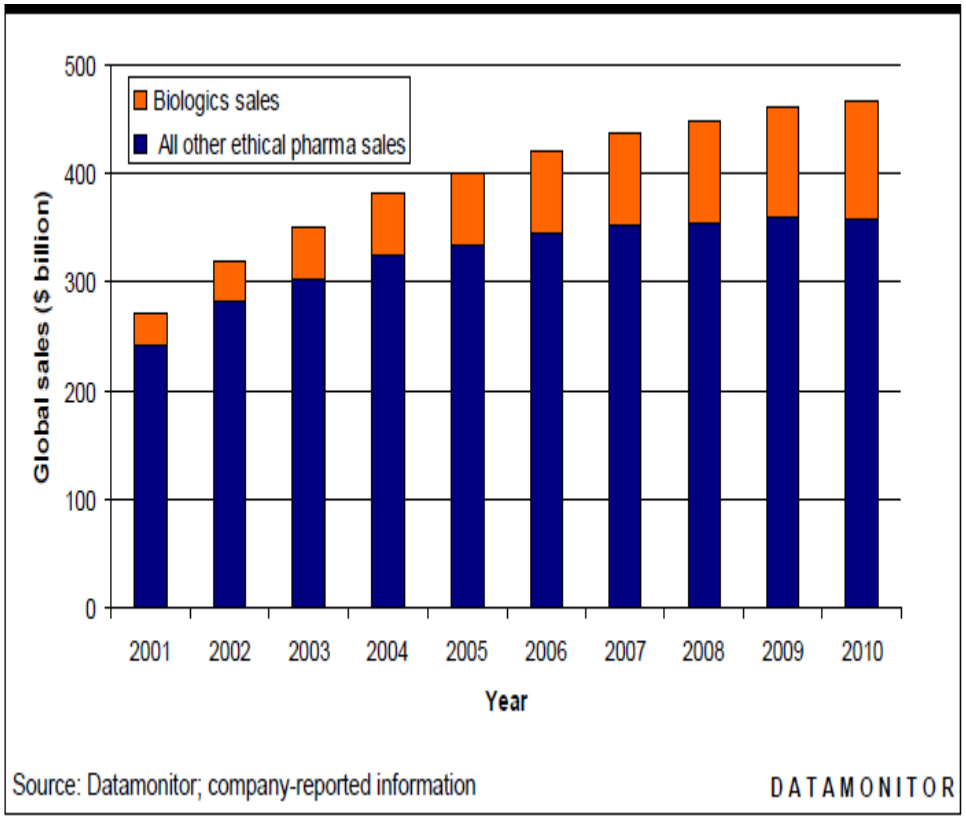
Pharmaceutical Biotechnology (Biopharmaceuticals)

The use of tissue cultures, living cells or cell enzymes to make a drug, therapy or diagnostic.

Advantages of Macromolecular (Protein) drugs

- ✓ **Very specific and extremly efficient**
- ✓ **Produced in mass quantity by using rDNA technology**
- ✓ **Easily formulated in liquid dosage form**
- ✓ **Relatively active at physiological temperature and conditions**

Global sales of biologics and total pharmaceuticals by 56 leading pharmaceutical companies, 2001-2010



Post Genome Project

1. **Genome:**
   35,000 - 40,000 Genes
2. **Proteome:**
   100,000 Proteins
3. **FDA approved:**
   only 450 protein drugs

Sales of biologics and total pharmaceuticals by 56 leading pharmaceutical companies, 2001-2010

	2003	2004	2005	2006	2008	2010	Growth 2003-04(%)	CAGR 2004-10(%)
Global biologics sales ($bn)	47.5	56.2	65.2	73.6	90.6	105.2	18.2	11.0
Global total sales ($bn)	351.4	382.2	400.4	421.0	448.1	466.4	8.8	3.4
Biologics as percentage of total sales (%)	13.5	14.7	16.3	17.5	20.2	22.6		
US biologics sales ($bn)	26.4	30.8	35.6	40.5	50.8	59.9	16.9	11.7
US total sales ($bn)	170.1	181.7	189.3	199.1	211.1	221.5	6.8	3.4
Biologics as percentage of total US sales (%)	15.5	17.0	18.8	20.3	24.0	27.0		
Rest of World biologics sales ($bn)	21.1	25.3	29.7	33.1	39.8	45.3	19.8	10.2
Rest of World total sales ($bn)	181.1	200.4	211.1	221.9	237.0	244.8	10.7	3.4
Biologics as percentage of total RoW sales (%)	11.7	12.6	14.1	14.9	16.8	18.5		

Source: Datamonitor; company-reported information

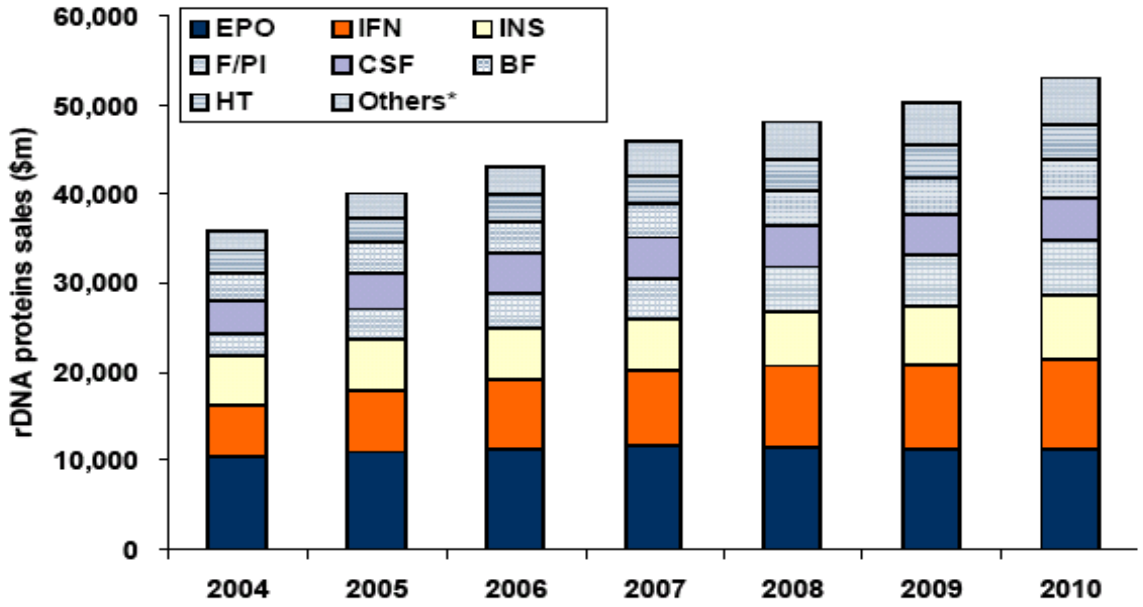
DATAMONITOR

Global Biotechnology Market 2006-2008

Biotechnology	Protein	Market size ($ billion)		
		2006	2007	2008(p)
Cancer, Arthritis Infection	Monoclonal Antibodies	20	27	33
Infections	Vaccines	15	19	25
Anemia	Erythropoietin	12	11.8	9.5
Autoimmune Inflammatory	TNF Blockers	10.6	13.5	18
Diabetes	Insulin	9	11	12.5
MS+ Hepatitis	Interferon	6.7	7.6	8
Growth, fertility	Hormones	6.5	7.4	8
Total Global Biotechnology Market		73	80	87

P: Projected,
IMS Top Line Industry Data 2007; Datamonitor

Recombinant products' revenue distribution according to protein class focus, 2004-10



BF = blood factors; CSF = colony-stimulating factors; EPO = erythropoietins; F/PI = fusion/protein inhibitors; HT = hormonal therapies; IFN = interferons; INS = insulins

Source: Datamonitor; company reports

DATAMONITOR

Problems with biopharmaceuticals

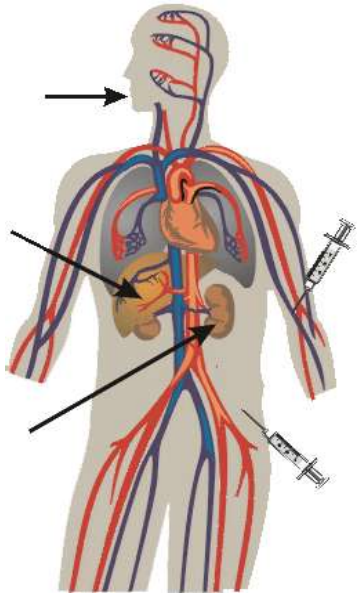
Orally inactive

Liver uptake

Proteolytic cleavage

Kidney filtration

Insolubility



-i.v. injection: very high blood levels initially

Immunogenicity/Antigenicity

Approaches to Bypass Enzymatic and Absorption Barriers

By:

- ✓ **Inhibition of enzymatic degradation by the co-administration of protease inhibitors**
- ✓ **Increasing permeability across the membrane by the co-administration of absorption enhancers**
- ✓ **Chemical modification of the drug substances**
- ✓ **Designing new pharmaceutical formulations**

Delivery Systems of Therapeutic Drugs

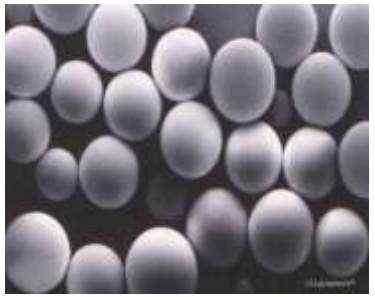
- ✓ **Entrapment or encapsulation**

  Hydrogels

  microspheres

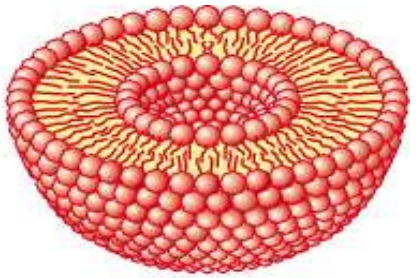
  Liposomes (200-300 nm)

  Microemulsions (<100 nm)



- ✓ **Bioconjugation**

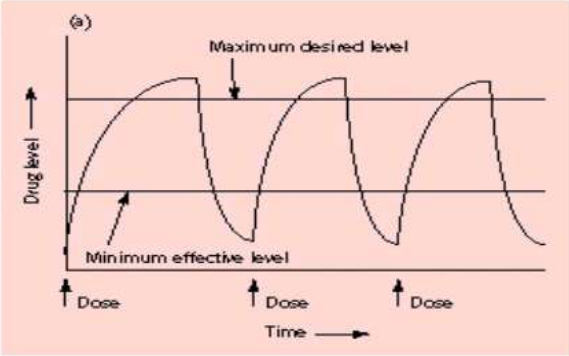
  PEG conjugates



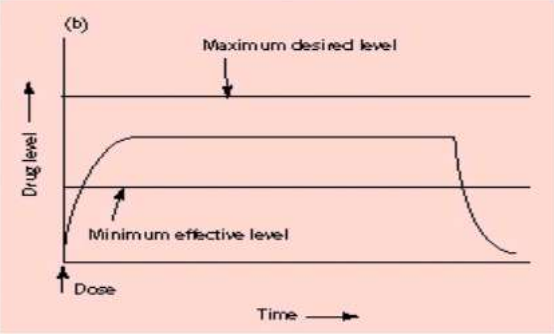
Development of Long acting Biopharmaceuticals

"Super Biosimilar or Biobetter"

- Enhanced activity duration for short half-life drugs
- Reduction of side-effects
- Less frequent dosing- improved patient compliance
- Protecting labile drugs- improved product stability
- Potential for extended patent protection



1st generation drugs



2nd generation drugs (long acting drugs)

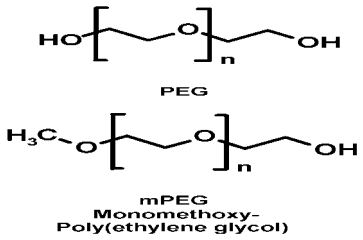
Long acting Biopharmaceuticals

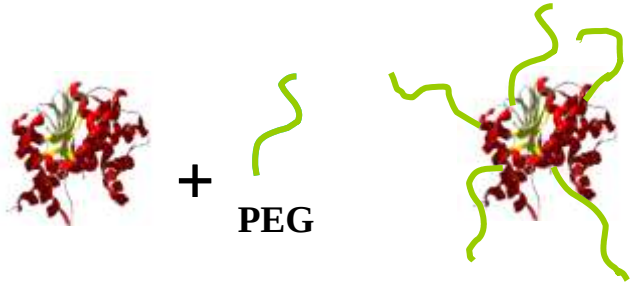
Name	Brand	Patent Expiry
Epoitin	Epogen/Procrit	2012/2013
Darbepoietin	Aranesp	2014
PEG-EPO	Mircera	Launched ‘07
Filgrastim	Neupogen	expired
Pegfilgrastim	Neulasta	2015
Interferon alpha	Intron a Roferon a	expired
PEG-interferon alpha	PEG-Intron PEGASYS	2014

Q: What is PEGylation?

A: PEGylation is a process whereby a substance called polyethylene glycol (PEG) is attached to a protein in order to extend protein activity.

PEG is used in everyday products, such as foods and cosmetics.

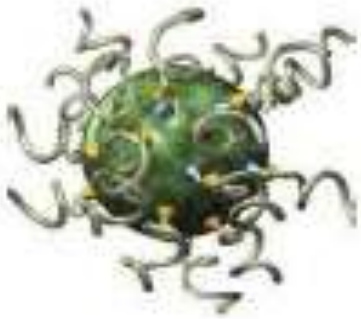




Attractive Features of polyethylene glycol(PEG)

- ✓**Excellent solubility**
- ✓**No toxicity in clinical dosage, non-immunogenic, non-antigenic**
- ✓**Non-biodegradable, non-biologically active**
- ✓**FDA approved polymer for the injection**

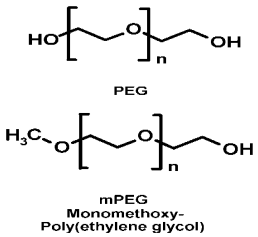
Why PEGylate?

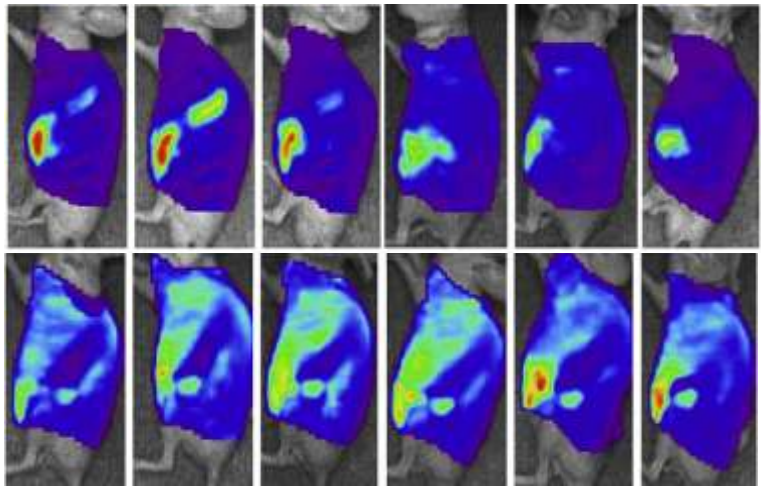


Therapeutic Protein Drugs

- Short half-life (1inj/day or 2-3 inj/week)
- Instability by enzymatic cleavage
- Immunogenicity/antigenicity (side effect)

PEGYLATION

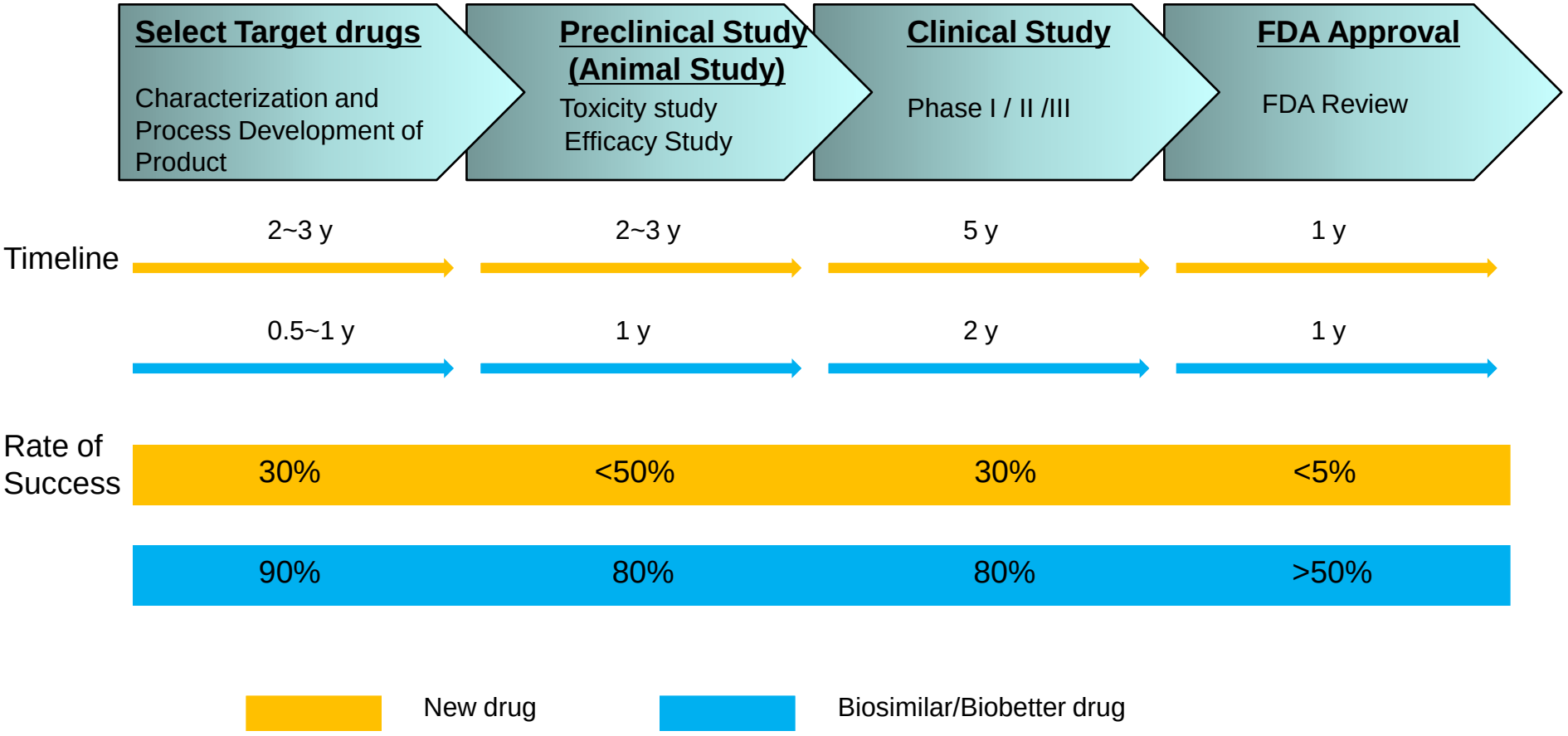




PEGylated Protein drugs

- Increased circulating half-life (10-100 fold)
- one inj/week or one inj/biweek
- Increased stability against enzymes
- Reduced side effect

Development of Biopharmaceutical drugs



The Federation of Korean Industries(FKI), 2009

Circulating Lives of Various Proteins Modified with Poly(ethylene glycol)

Enzyme	Source	Route	Host	$t_{1/2}$native	$t_{1/2}$mPEG
Adenosine deaminase	calf intestine	IV	Balb/c mice	30 min	28 h
Asparaginase	E.coli	IP	rats	2.9 h	56 h
Arginase	bovine liver	IV	B6D2 mice	1 h	12 h
Catalase	bovine liver	IV	Long-Evans mice	10 min	> 4 h
Superoxide dismutase	bovine RBC	IV	Lewis-male mice	5 min	4.2 h
Uricase	*Candida utilis*	IV	human	< 3 h	8 h

PEGs in ACTION

- **8 Approved and Marketed Products**

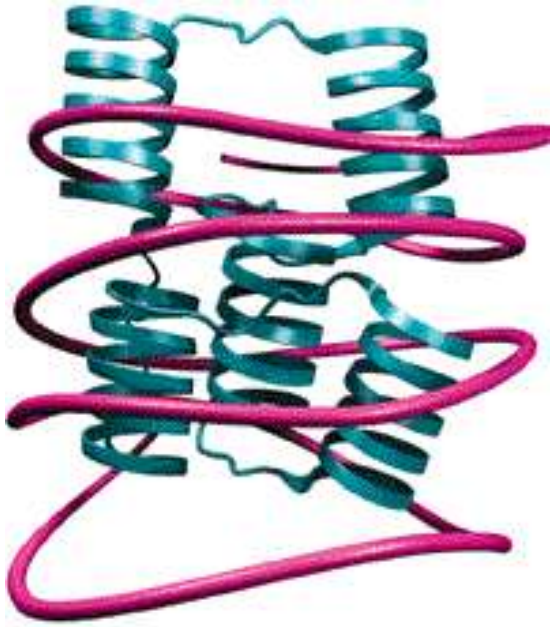
  - PEG-ADA (Enzon, 1990)
  - PEG-Asparaginase (Enzon, 1994)
  - Neulasta (Amgen, PEG-G-CSF)
  - PEGASYS (Nektar/Roche, peginterferon, 2002)
  - PEG-Intron (Enzon/Schering-Plough, peginterferon, 2001)
  - Somavert (Pharmacia, pegvisomant)
  - Macugen (Pfizer, pegaptanib, age-related macular degeneration, 2004)
  - Mircera (Roche, PEG-EPO, 2007)

- **Under Development**

  - PEG-Superoxide Dismutase
  - PEG-Hemoglobin (Blood Substitute)
  - PEG-camptothecin
  - PEG-hGH variant (Genentech)
  - PEG-GMCSF (PolyMASC)
  - PEG-IL-8 mAb (Genentech)

Interferon-α

- Treatment of chronic Hepatitis B and C, and cancers
- Fast absorption
- Short half-life due to rapid metabolism and renal clearance
- Administered everyday or 3 times/week

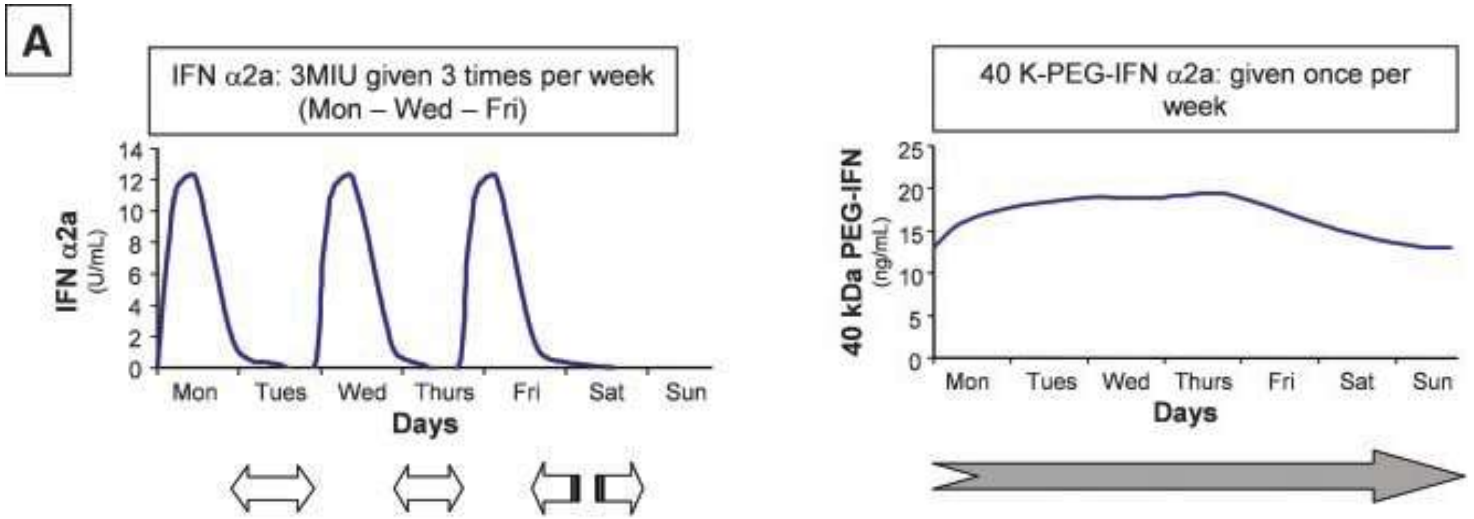


PEG-Interferon α

- Developed by Schering-Plough/Enzon (2001) and Roche/Nektar (2002)
- Extended serum half life to 7-10 folds
- Reduced immunogenicity/antigenicity by PEG conjugation
- Administered once a week

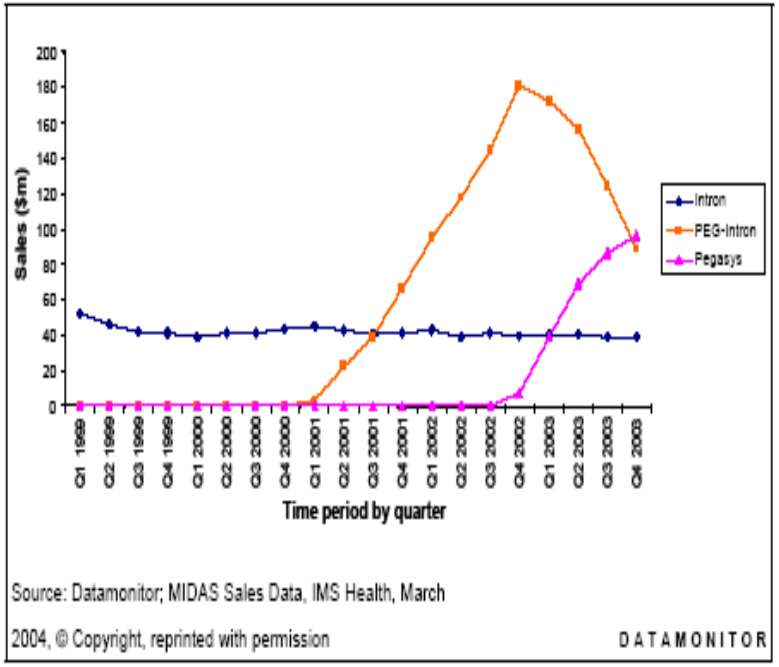
- Total Market: over $3 billion/year

PK profile of PEG-Interferon



Sales of Intron, PEG-Intron and Pegasys in the US:

Intron's sales have been static, while PEG-Intron's sales grew Rapidly following its launch, but has been declining heavily since 2003



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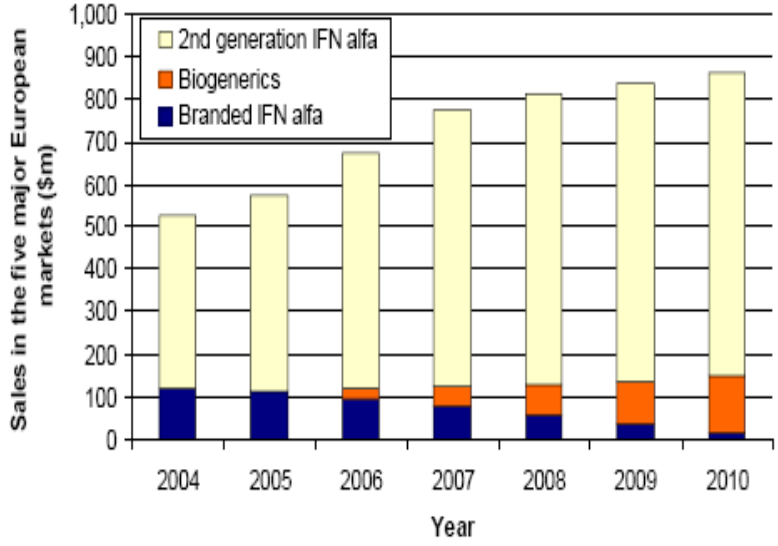

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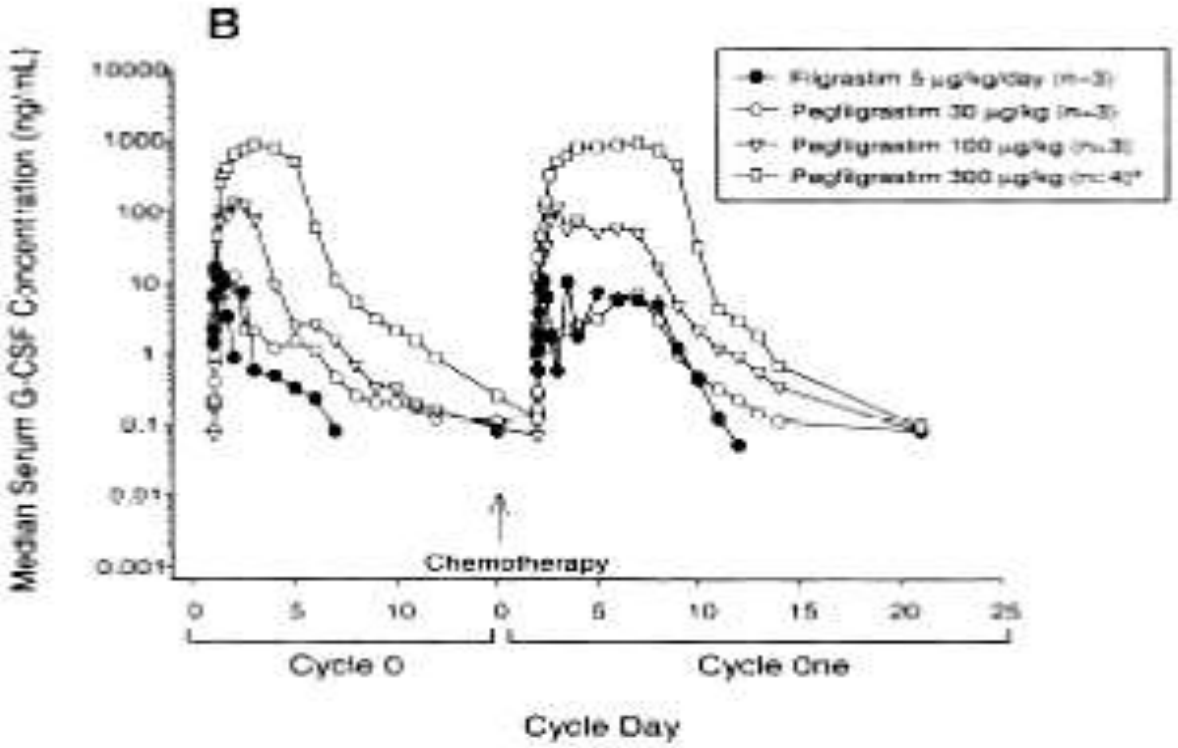
G-CSF
(Granulocyte Colony-Stimulating Factor)

- Treatment of myelosuppression associated with chemotherapy
- Required daily administration for 10 days to produce a sustained increase in granulocytes during chemotherapy (4-8 hrs of half-life)
- Near $1.8B sale (2006)

PEG-G-CSF
(PEG-Granulocyte Colony-Stimulating Factor)

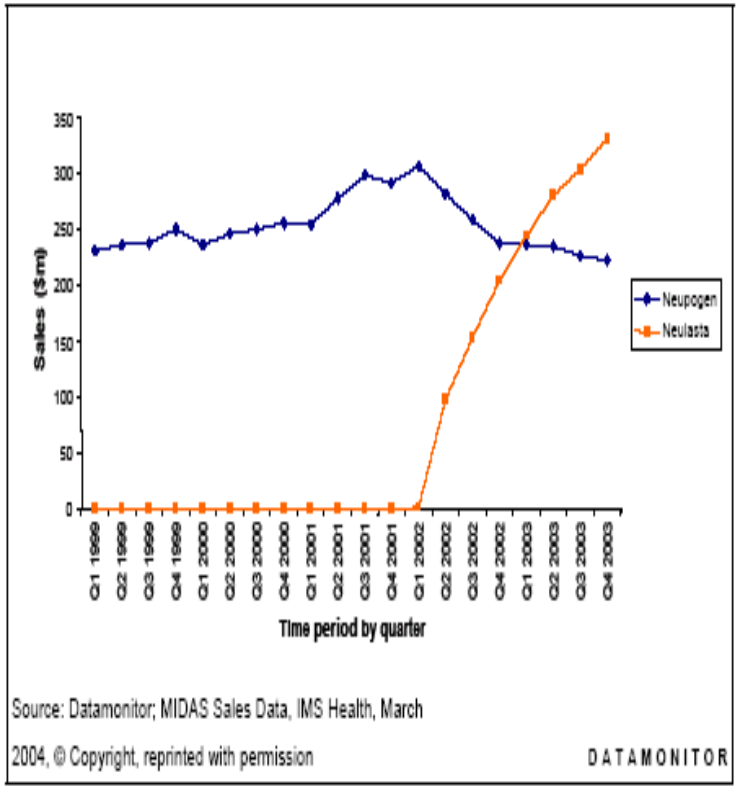
- Covalent conjugate of rG-CSF with polyethylaene glycol
- Reduced renal clearance and prolonged persistence in vivo (15-80 hrs of Half-life)
- Required only one administration during chemotherapy
- Launched in 2002 (Neulasta™)
- $2.7 B sale (2006)

Pharmacokinetics of PEG-G-CSF (Neulasta™)



Sales of Neupogen and Neulasta in the US:

Neulasta's sales were greater than Neupogen a year after its launch



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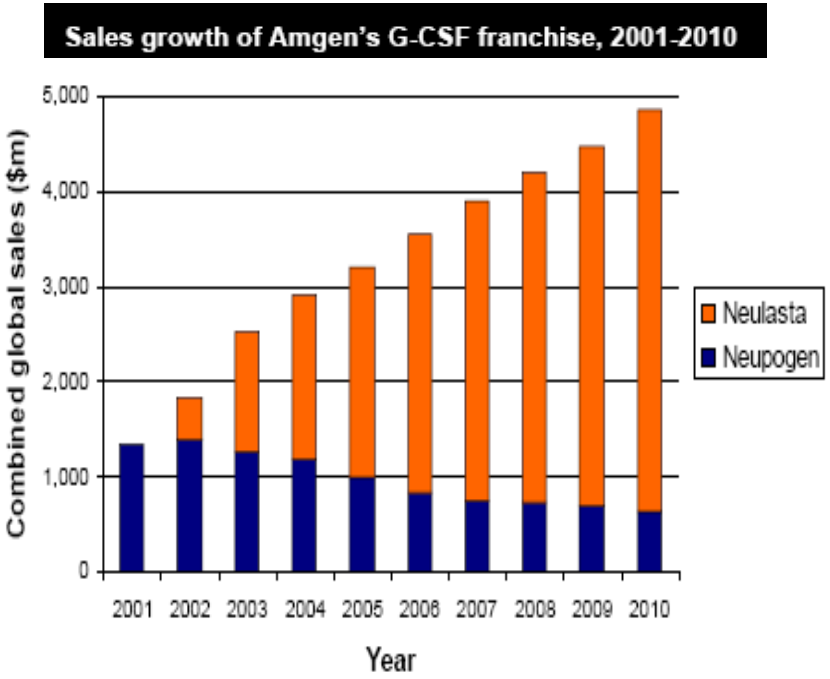

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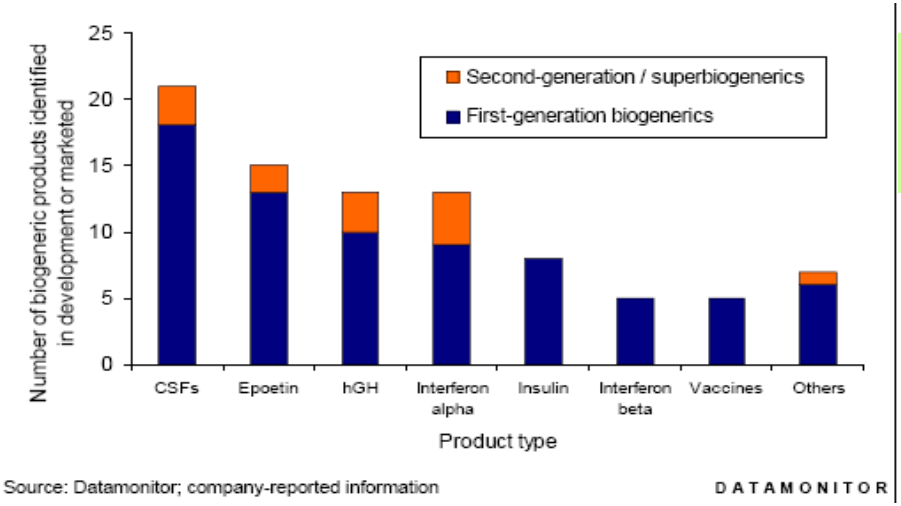
Conclusions



PEGylation:

- ✓ Prolongs circulating half- life of protein drugs
- ✓ Reduces toxicity and improves therapeutic efficacy
- ✓ Potential technology for the next generation of protein drugs
- ✓ Still many more protein drugs to be PEGylated to improve the drug efficacy
- ✓ Extends patent life of previously approved drugs

Thank you for your attention !

http://www.biopolymed.com