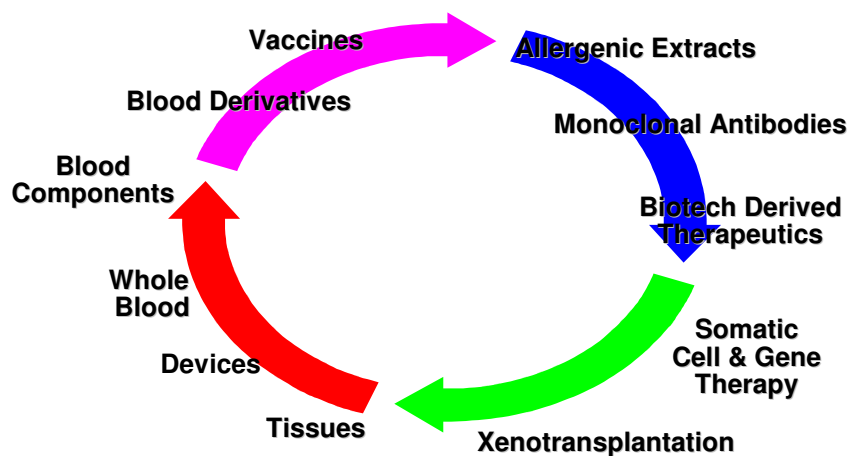


Biotechnology Medicinal Products: Opportunities and Challenges

October 2, 2007

Dr. Kenneth B. Seamon
Institute of Biotechnology
University of Cambridge

BIOLOGICAL PRODUCTS

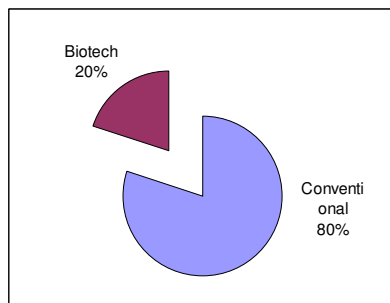


Different Classes of Biotechnology Products

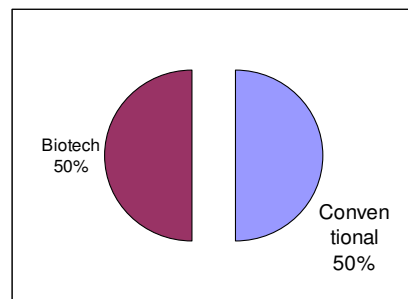
- Hormones
- Cytokines
- Monoclonal Antibodies
- Therapeutic Enzymes
- Clotting Factors
- Vaccines
- *Immunotherapy (Tumor vaccines)*
- *Cell and Gene Therapy*
- *Antisense and siRNA*

The Healthcare Biotech Industry

Medicines on the market

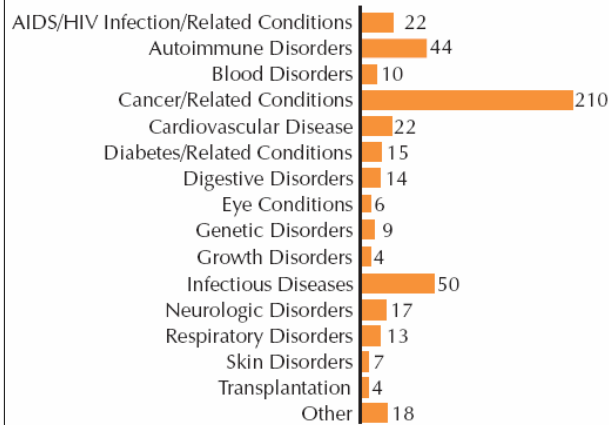


New medicines in development



Source: European Commission

Biotechnology Medicines in Development



PhRMA Survey 2006



Multiple Sclerosis



Cancer



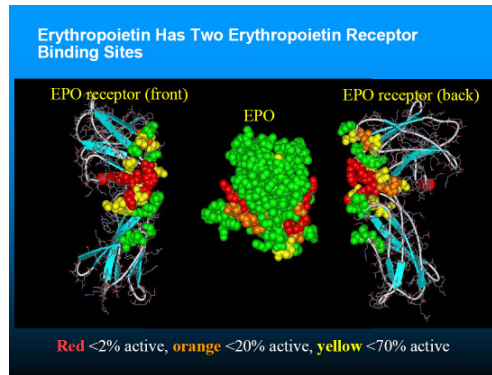
Rheumatoid Arthritis

The Growing Importance of Biotechnology

- Biotechnology drugs have been proven to be safe and effective with an excellent record of patient satisfaction and safety
- Biotechnology has produced medical treatments for some of the most serious diseases
- More than 325 million people worldwide have been helped by more than 155 biotechnology drugs and vaccines
- Biotech is to meet unmet medical needs with innovative treatments
 - Treatments available for just 10 000 of the 30 000 known diseases
 - Increase in the number of disease targets for conventional drug therapy from 500 today to nearly 10 000 in the future
 - 20-30 million Europeans affected by 5000 rare diseases:
 - Powerful tools to develop diagnostics and treatments for orphan diseases
- Biotechnology therefore is a success story

Opportunities for Biotechnology Medicines

- Unique specificity
- Identical or mimic naturally occurring molecules
- Stimulate (or inhibit) natural biochemical pathways for eliciting cellular and pharmacological responses



What Are Biotechnology Medicines?



Biotech medicines often replace or supplement a natural protein produced by the body, satisfying medical needs previously unmet by chemical medicines

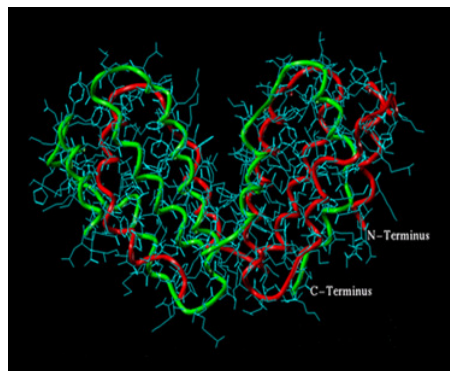
More than 325 million patients worldwide have been helped by biotech medicines

Differences between Chemical Drugs and Biotechnology Medicines



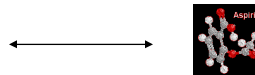
Chemical drugs	Biotech medicines
Made by chemical synthesis	Recombinant proteins Made by living cells <ul style="list-style-type: none"> Unique cell lines, from bacteria, yeast, or mammals
Defined structure and easy to characterize	Heterogeneous structure, difficult to characterize, mixtures of related molecules
Relatively stable	Variable; sensitive to conditions
Usually taken by mouth and prescribed by a general practitioner	Usually injected and prescribed by specialists

Biotech Medicines are More Complex than Chemical Medicines



Interferon Beta
MW 19'000D

- Large numbers of molecular components
- Bigger molecular size
- Cannot be uniquely described using a simple set of tests



Aspirin:
MW 180D

Protein Structure: Building A Biotech Medicine



Primary:
Amino Acid Sequence



Secondary:
Interaction of Amino Acids

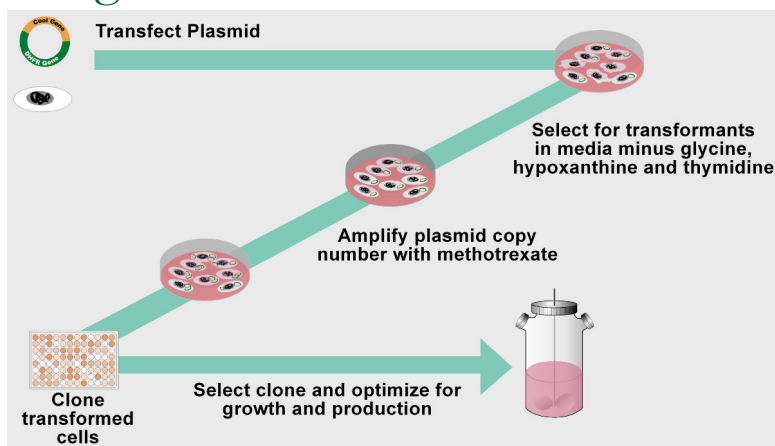


Tertiary:
Hydrophobic and Hydrophilic Interactions, Disulfide Bonds, and Posttranslational Modifications



Quaternary:
Interactions With Other Proteins

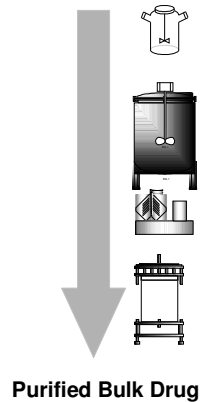
Manufacturing Starts with a Unique Living Cell



Main Manufacturing Process



Steps



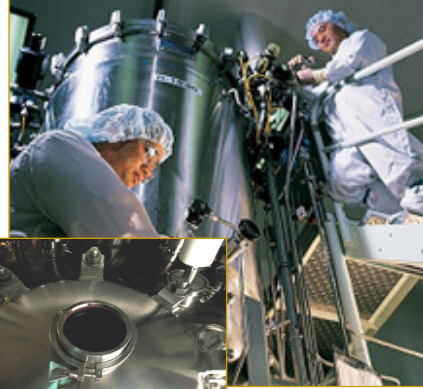
Unit Operation	Specific to Product
Cell Expansion	Cell line, growth media, method of expansion
Cell Production in Bioreactors	Cell line, growth media, bioreactor conditions
Recover through filtration or centrifugation	Operating conditions
Purification through chromatography	Binding and elution conditions
Characterization and Stability	Methods, reagents, reference standards

Characteristics Of the Manufacturing Process

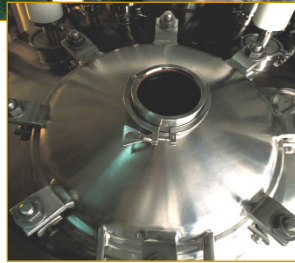
- Products are made from living cells
- Takes months, not weeks, to produce a run
- Cost per run can be millions of euros
- To obtain consistent results, precise controlling necessary



New Biotechnology Production Facilities



- Significant Time and Investment
- 5 years and ~\$1B

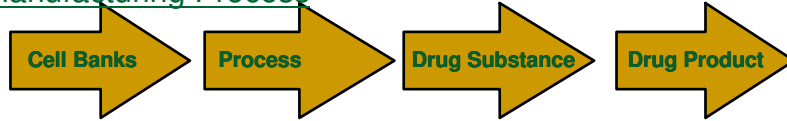


Unique Characteristics of Biotechnology Medicines

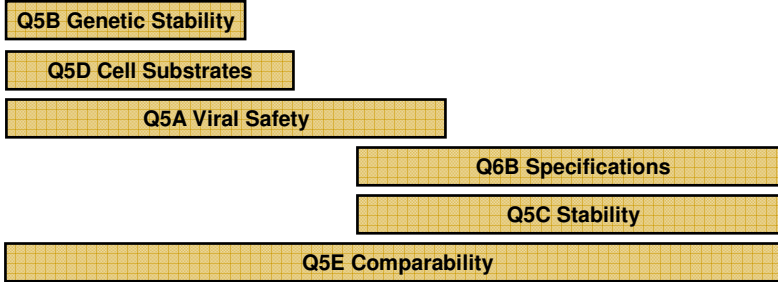
- Species specificity limits standard preclinical models for safety testing
- Must be given parenterally through intravenous (i.v.), subcutaneous (s.c.), or intramuscular (i.m.)
- Products usually require storage under refrigerated or frozen conditions
- Manufacturing is significantly more complex and a critical factor in safety and efficacy
- Products can lead to immunogenicity with significant long term effects

Regulatory Quality Guidelines through International Conference on Harmonisation

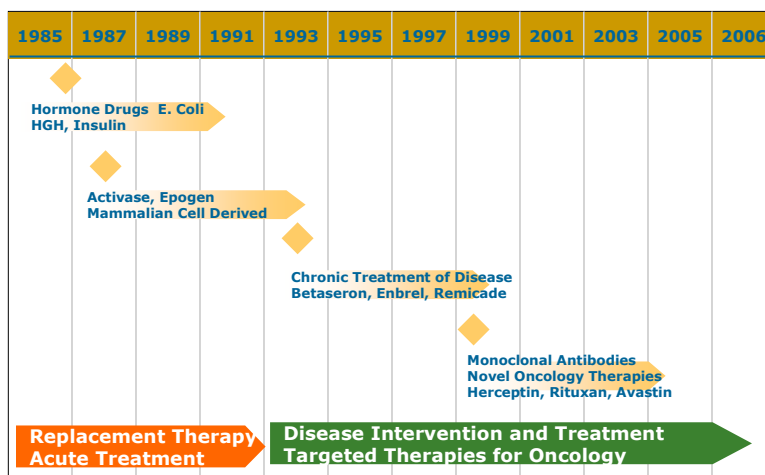
Manufacturing Process



ICH Documents

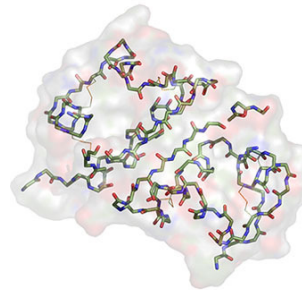


Evolution of Protein Therapeutics



Hormone Replacement

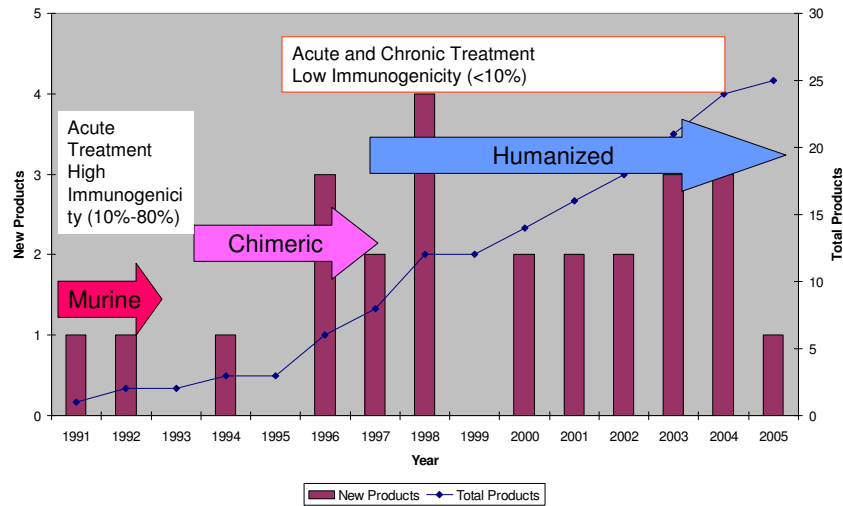
- Therapeutic Need
 - Replace hormones derived from animal species or cadavers
 - Eliminate immunological and infectious disease concerns
- Therapeutic Basis
 - Copy naturally derived hormone
 - Insulin and Growth Hormone
- Therapeutic Benefits
 - Immunogenic concerns minimized but not totally alleviated for Insulin
 - Concerns about CJD eliminated regarding hGH



Monoclonal Antibodies Represent One of the Larger Classes of Products in Development

- First described by Köhler and Milstein in 1975
- Sensitive and Specific (Magic Bullets?)
 - Numerous technologies to generate specific antibodies against human epitopes
- Engineered to be humanized
- Manufacturing using standard mammalian cell bioreactors and cell lines
- Multiple mechanisms to provide therapeutic benefit
 - Effector function
 - Kill or eliminate target cells
 - Bind and neutralize biological molecules (and toxic small molecules)

Therapeutic Monoclonal Antibodies



US Approvals compiled from PhRMA 2006 Medicines in Development Biotechnology

Complexity of Monoclonal Antibody

Potent effector molecules, conjugate, and/or glycosylation sites

Disulfide bond

Tumor-targeting regions

Comments:
 Non oral ROA
 Large size
 complex 3-D structure
 SAR difficult
 Variant forms
 No metabolites

From: M. Sanicola, V. Bailly

biogen idec

A New Treatment for Rheumatoid Arthritis Based on Monoclonal Antibody Structure

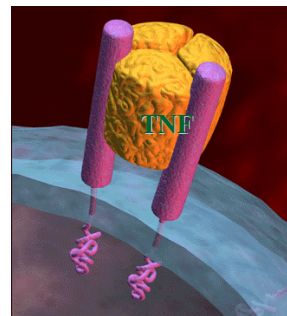
- Rheumatoid Arthritis is a chronic inflammatory disease characterized by significant morbidity and increased mortality
- It affects 1% of population
 - 3:1 female to male
 - Peak onset 30 - 40 years of age
- Many patients do not respond or cannot tolerate standard Disease Modifying Anti-Rheumatic Drugs (DMARDS)



Clinical Consequences of TNF in Rheumatoid Arthritis

Binding of TNF to cell-surface receptors initiates a variety of inflammatory events

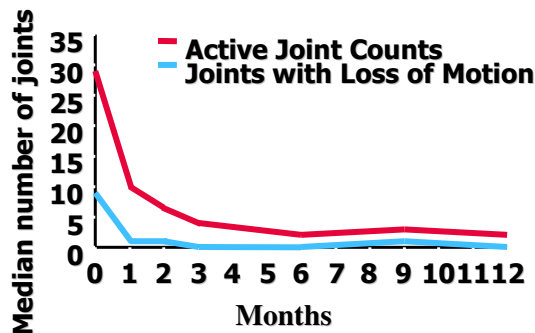
- Pain
- Fatigue
- Stiffness
- Impaired function
- Joint destruction



Cell-surface receptor

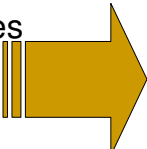
Margolies GR et al. In: Strand V et al, eds. *Novel Therapeutic Agents for the Treatment of Autoimmune Diseases*. Marcel Dekker, 1997:141-153.

ENBREL a Soluble TNF Receptor Blocks TNF Function



- Mimics naturally occurring receptors that bind TNF
- Blocks TNF from binding at sites
- Blocks TNF from stimulating inflammation at joints

Biotechnology Innovation and Diversity: A unique Resource for Providing Novel Solutions to Diseases

- Diversity in US and Europe Companies
 - >400 public
 - ~2800 private
 - Core Competencies
 - Molecular biology
 - Virology
 - Immunology
 - Infectious diseases
 - Uniquely positioned to address solutions to global health issues
- 
- Affordable, simple diagnosis of diseases
 - Recombinant technologies to develop vaccines against infectious diseases
 - Technologies for more efficient drug delivery systems
 - Sequencing pathogen genomes to understand their biology and to identify new antimicrobials
 - Bioinformatics to identify drug targets
 - Recombinant technology to make therapeutic products (e.g. Insulin, interferons) more affordable

The Impact of Vaccines

Disease	Base Morbid.	1998 Morbid.
Diphtheria	175, 885	1
Polio (paralytic)	16, 316	0
Measles	503, 328	89
Rubella (CRS)	823	5
Hib	20, 000	54
Smallpox	48, 164	0

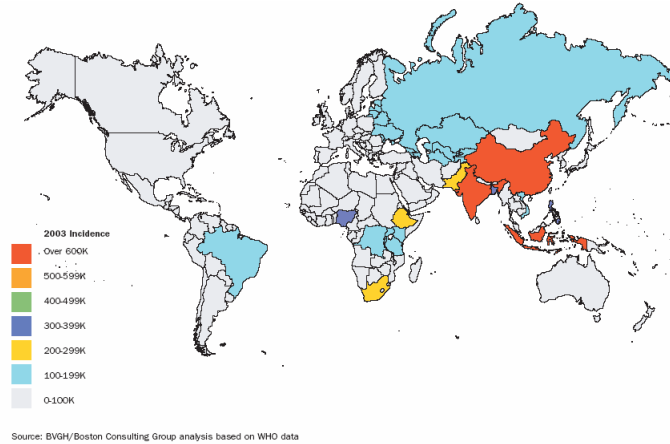
MMWR 48(12), 243-48 (1999)

Bill Egan, Ph.D., FDA, CBER, 2002

Examples of New Vaccines

- Hepatitis B
 - Hepatitis A
 - Pneumococcus
 - Rotavirus
 - HPV
 - Dengue Fever
 - Meningitis
 - West Nile Virus
 - Cholera
 - HIV
- On Market Vaccines
- In Development

Global Incidence of Tuberculosis



Examples of Current Approaches to More Effective Tb Vaccines

Core technology	Development Stage					Company
	Research & Discovery	Pre-clinical	Ph I	Ph II	Ph III	
1. Live Recombinant + Pox virus as vector	█	█	█	█	█	Oxford University
2. Recombinant protein + MPL adjuvant	█	█	█	█		GSK & Aeras
3. Recombinant Fusion-protein Ag85B & ESAT-6	█	█	█	█		SSI & Intercell
4. Aeras 403	█	█	█	█		Aeras
5. Recombinant Protein PER, C6 & AdVac	█	█	█	█		Crucell & Aeras
6. Ag85B, Ag10.4	█	█	█	█		SSI, Intercell & Aeras
7. Attenuated live TB	█	█	█	█		Jacobs / Einstein
8. Live rBCG (r-BCG ΔureC:Hly)	█	█	█	█		Vakzine Projekt Management (Max-Planck)

Source: BVGH

Biotechnology derived vaccines in development

Summary: Impact on Patients

- Biotechnology Medicines provide unique and promising opportunities to provide treatments for serious and life threatening diseases and for providing new treatments for unmet public health needs
 - They will increasingly become accessible, and provide patients and doctors with new treatment options
 - Quality and safety issues are key and different from traditional chemical drugs
 - Patients will achieve tremendous benefit from investments in these new medicines
-

Supplementary Information

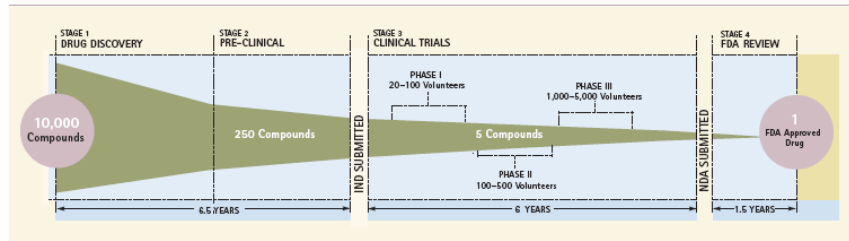
Immunogenicity – A Unique Safety Issue For Biotechnology Medicines

- Therapeutic proteins have the potential to induce antibody responses
 - Initial response to therapeutic protein
 - Later broad response incl. endogenous protein
- In many cases, no clinical consequences but antibody-related reaction can be serious, even life-threatening
- Immunogenicity cannot be predicted with preclinical or non-human studies
 - Clinical studies required pre-approval
 - Robust monitoring after approval to assure safety

Consequences of Immunogenicity

- Current Experience
 - Anaphylaxis – rare
 - Serum sickness – rare
 - Immune complex disease – rare
 - Changes in immune function – rare
- Significant Consequences of Immunogenicity
 - Loss of activity due to rapid clearance
 - Extended pharmacologic response due to extended PK profile
 - Loss of activity of product due to neutralizing antibodies
 - Loss of activity of endogenous molecules due to cross reaction

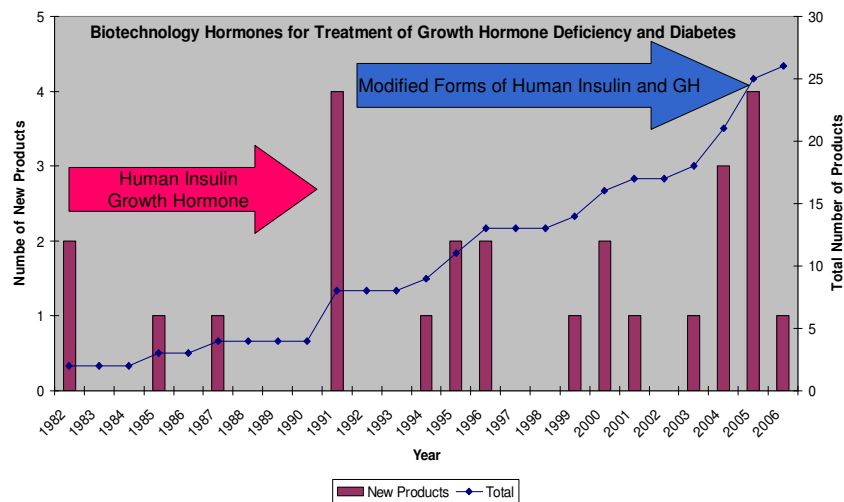
Biotechnology Can Significantly Facilitate the Development of Therapeutic Medicines



Source: www.innovation.org

- It takes over ten years to bring one drug to market
- One out of about 10,000 drug candidates actually achieves approval
- Biotechnology drug candidates are based on biologically active molecules in the body
- Biotechnology derived products are highly active with unique specificity

Human Recombinant Insulin and Growth Hormone

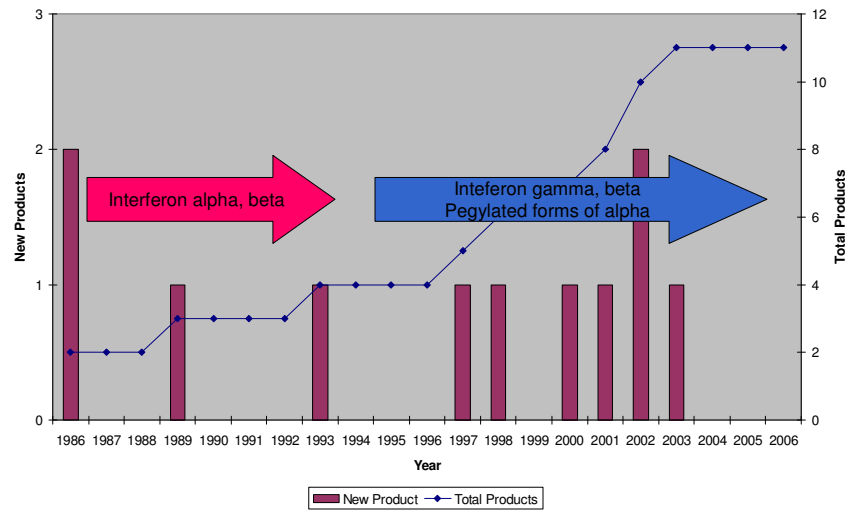


US Approvals compiled from PhRMA 2006 Medicines in Development Biotechnology

Interferons

- Therapeutic Benefits
 - Leukemia, melanoma, Kaposi sarcoma
 - Hepatitis B and C
 - Multiple Sclerosis
- Immunogenicity while present has not been a concern
- Product Lifecycle
 - Pegylated versions for improved dosing
 - Combination with antiviral medication

Recombinant Interferons

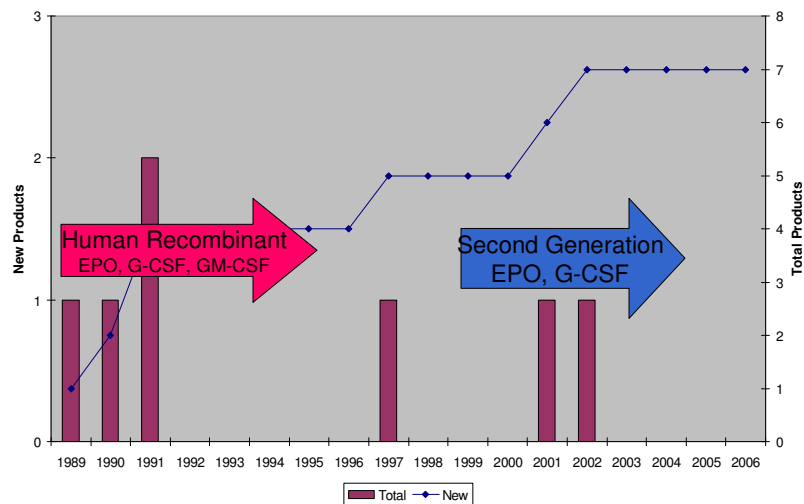


US Approvals compiled from PhRMA 2006 Medicines in Development Biotechnology

Therapeutic Recombinant Cytokines for Replacement Therapy

- Erythropoetin
 - Correction of anemia associated with chronic renal disease
 - Damaged kidneys cannot produce erythropoetin to stimulate hematopoiesis and red blood cells
 - Patients require transfusions
- Erythropoetin, Granulocyte Colony Stimulating Factor, Granulocyte-Macrophage Colony Stimulating Factor, Interleukin-11
 - Treatment of anemia, neutropenia, and thrombocytopenia associated with chemotherapy
 - Chemotherapy suppresses the marrow resulting in decreased production of red blood cells
 - Reconstitution of bone marrow after transplants results in time lag for neutrophil production putting patients at serious risk of infection and death

Recombinant Therapeutic Cytokines



US Approvals compiled from PhRMA 2006 Medicines in Development Biotechnology