FARMACI INNOVATIVI

Qualità **E**fficacia **A**ppropriatezza

Garanzia dell' universalità delle cure sul territorio nazionale

I Biosimilari

CAMERA DEI DEPUTATI- Palazzo Marini
26 giugno 2008

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Istituto Nazionale Tumori Regina Elena

IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA

Biotecnologia:
La Rivoluzione Invisibile

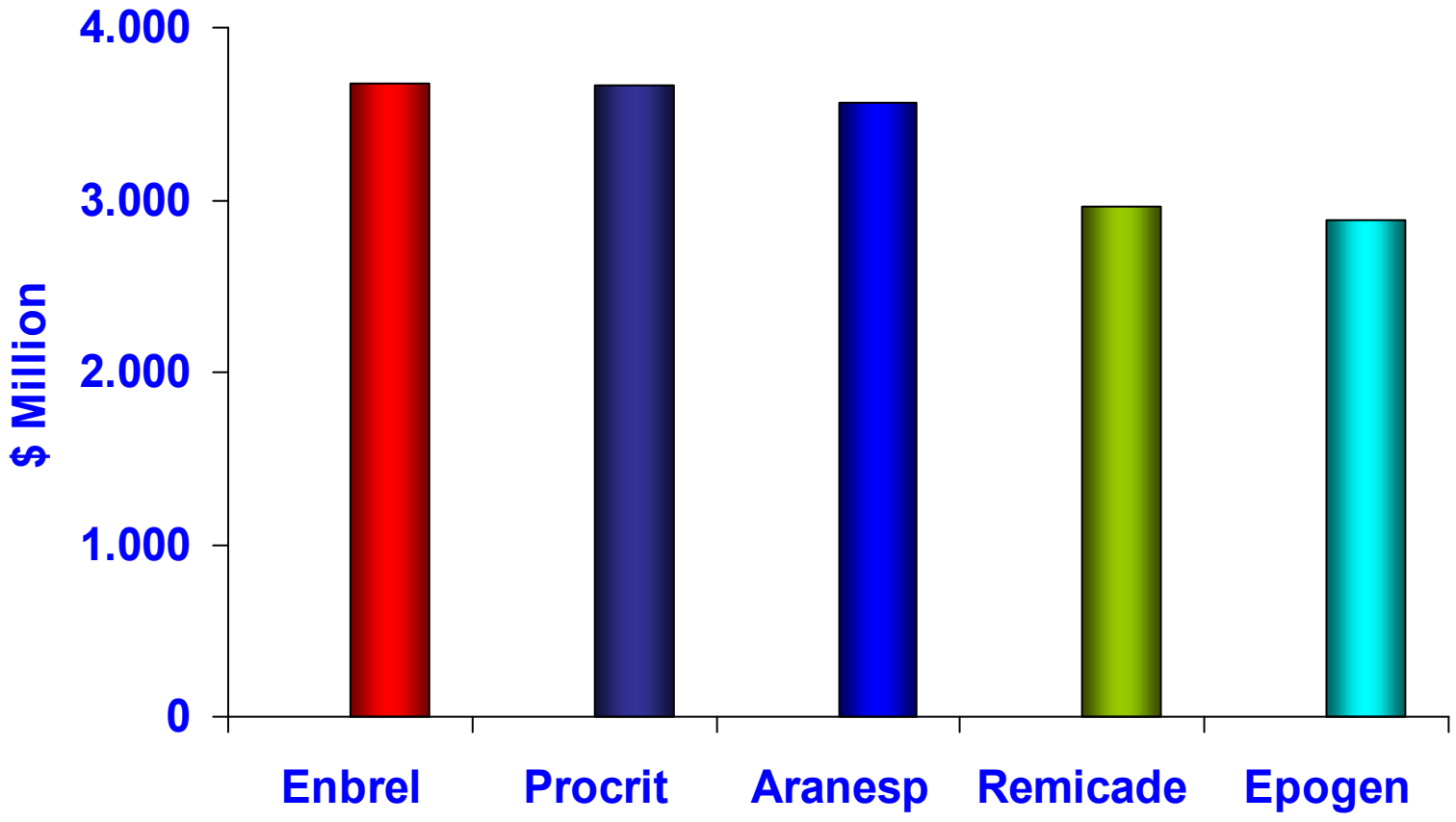
- ✓ L'innovazione farmaceutica migliora la qualità e l'aspettativa di vita

- ✓ La biotecnologia è la prima risorsa di innovazione farmaceutica
  - ➢ 50-70% dei nuovi farmaci derivano dall'industria biotecnologica

Farmaci Biotech

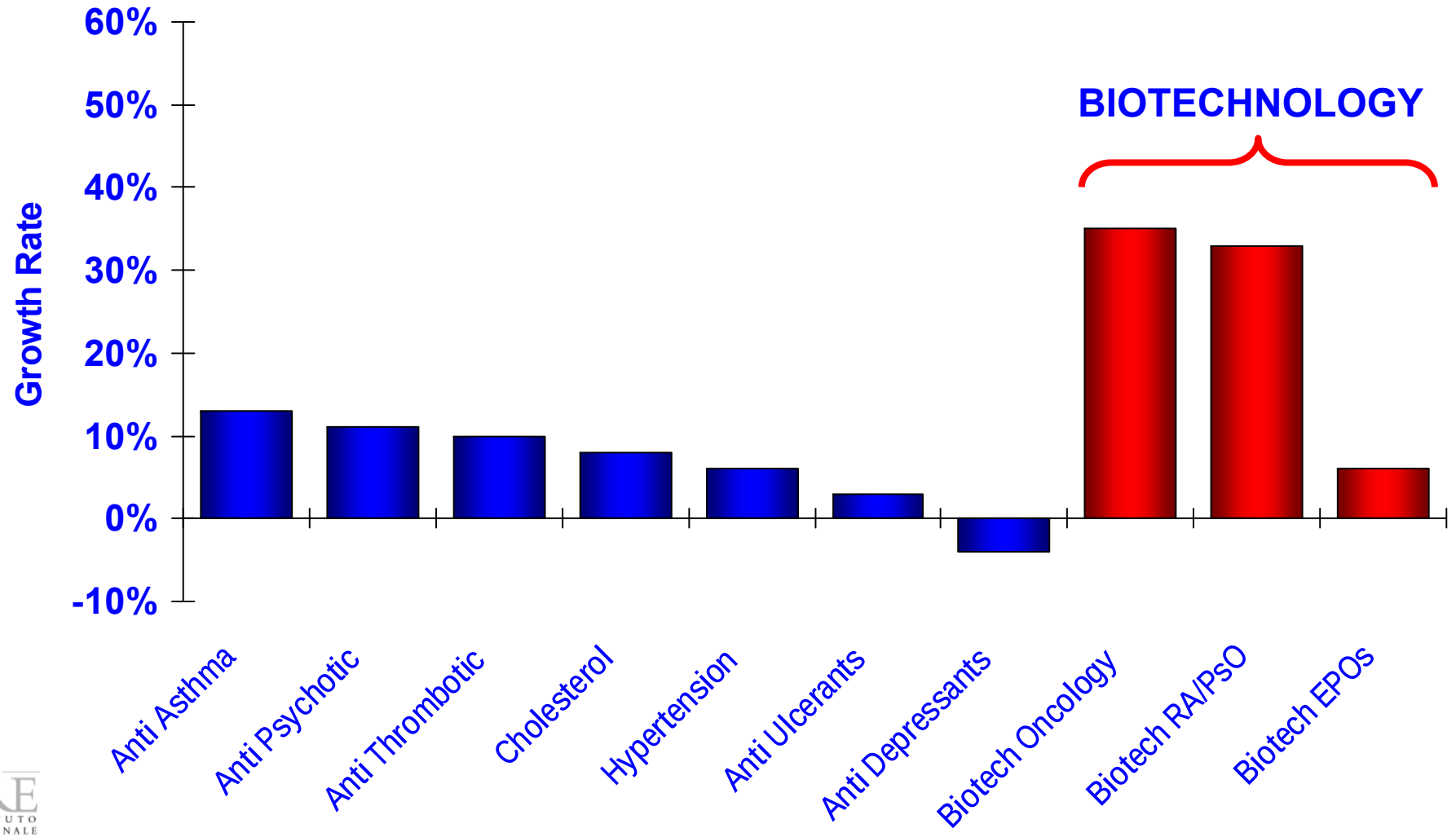
- ✓ Nel 1982 approvazione del primo prodotto biotecnologico
- ✓ Dal 2000, i farmaci biotech sono oltre il 25% di tutti i nuovi farmaci approvati
- ✓ Nel 2003 le vendite di Epogen, “biotechnology’s best-selling drug”, sono state di $2.4B
- ✓ Più di 190 farmaci biotech sono al momento sul mercato
- ✓ Circa 300 prodotti biotech sono in clinical trials di Fase III

5 dei top 20 prodotti farmaceutici sono prodotti con biotecnologie



Fonte: IMS data, 2005

La maggiore crescita economica si osserva per farmaci biotecnologici



Fonte: IMS data, 2005

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Farmaci Biotech: Targeted therapies

Definizione…

✓Nuove tecnologie e farmaci permettono di attaccare direttamente specifiche cellule tumorali ed interferire con le normali funzione cellulari

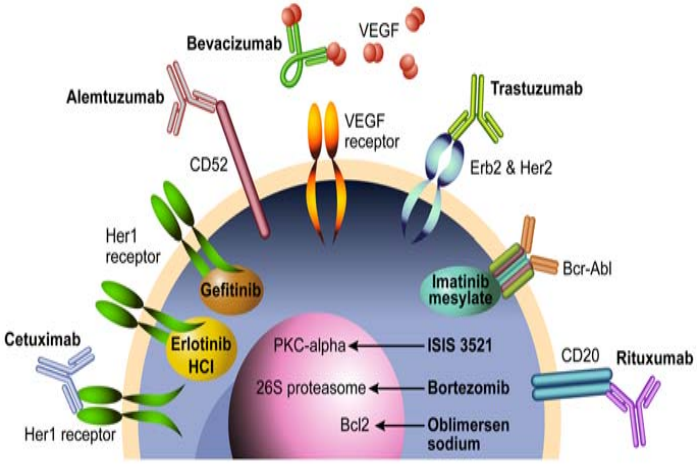
Come lavorano…

✓"target" si riferisce ad una parte della cellula tumorale

Cosa significa nel trattamento dei tumori…

✓Migliore qualità di vita dovuta a minori effetti collaterali

Targeted Therapies



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OVERVIEW

- What are biopharmaceuticals
- “The process is the product”
  - Overview of biopharmaceutical manufacturing
- Immunogenicity
  - Prime safety concern for Biosimilars
- Current regulatory issue
- Conclusion

Terminology

Biopharmaceutical (Biological)

Therapeutic agent containing Biotechnology-derived protein as active substance

Innovator

Reference biopharmaceutical

Biosimilar (Follow-on biologic)

A follow-on or attempted copy of an originator biopharmaceutical

Biosimilars Are Not Generics

- **Follow-on products of traditional chemical pharmaceuticals are exact chemical copies**
  - these are true generics

- **Follow-on products of innovator biological pharmaceuticals are only similar "copies"**
  - There are no "biogenerics"
  - There are only similar products i.e. "Biosimilars"

Generic And Biosimilar

” All that glitters is not gold”

William Shakespeare, The Merchant of Venice

- **Generic**

❑ A generic drug is identical to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use

- **Biosimilar**

❑ A version of biologic medicinal product that is similar, but not identical to, the originator product

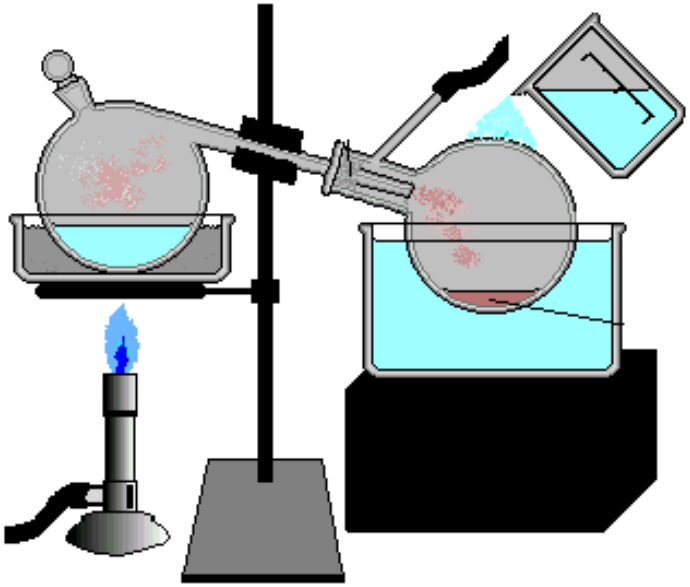
Generic And Biosimilar

- Chemical product-Generic - Easy to manufacture
- Biopharmaceutical-Biosimilar - Complex Challenge

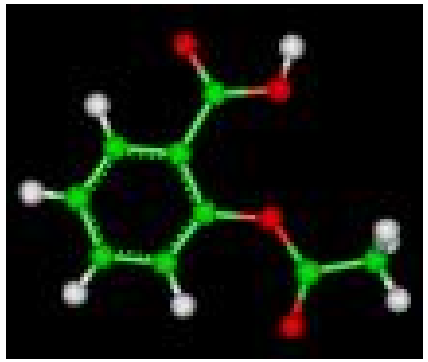
Farmaci sintetici vs biotecnologici

Farmaco Sintetico

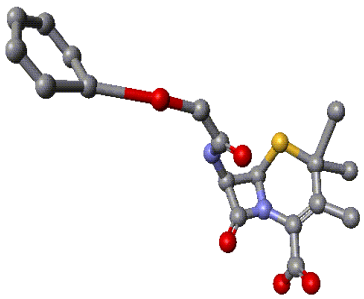
Produzione



Prodotto



Aspirina

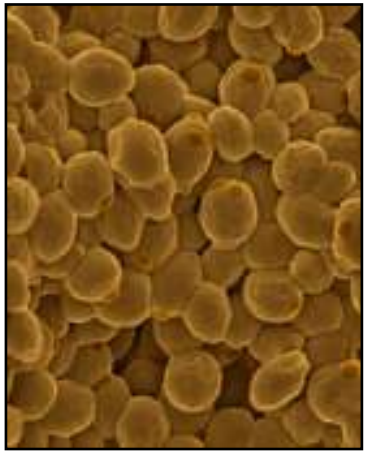


Penicillina

Farmaci sintetici vs biotecnologici

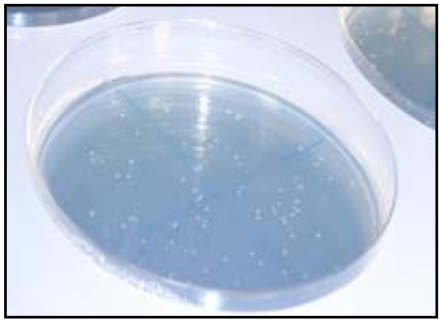
Farmaco Biotecnologico

Produzione



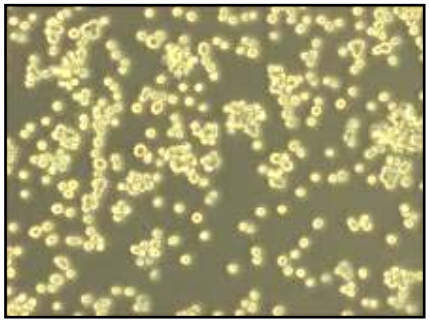
Lieviti

Animali Transgenici



Cellule Batteriche

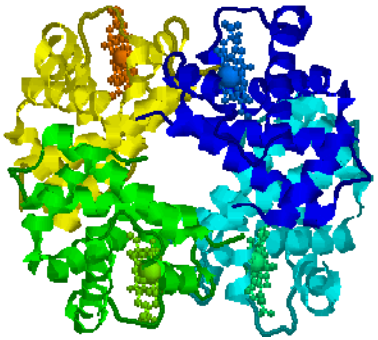
Piante Transgeniche



Cellule Animali

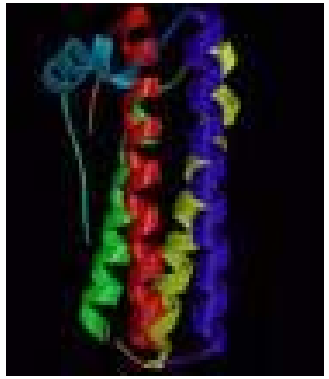
Biopharmaceuticals: the Process is the Product

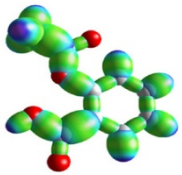
The protein Challenge: A Scientific Perspective



structure

size



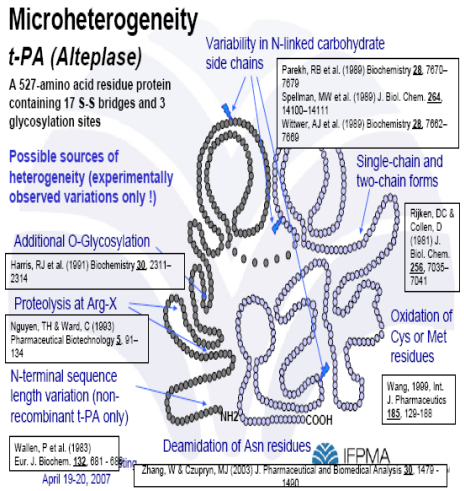


G-csf

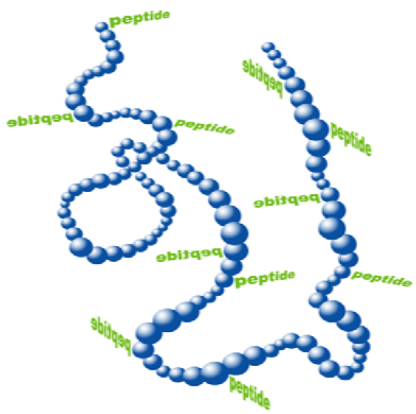
aspirin

modification

stability



Glycosilation, Acylation, etc

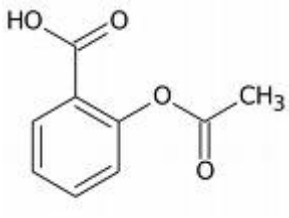


Denaturation, aggregation, degradation, oxidation

Structure

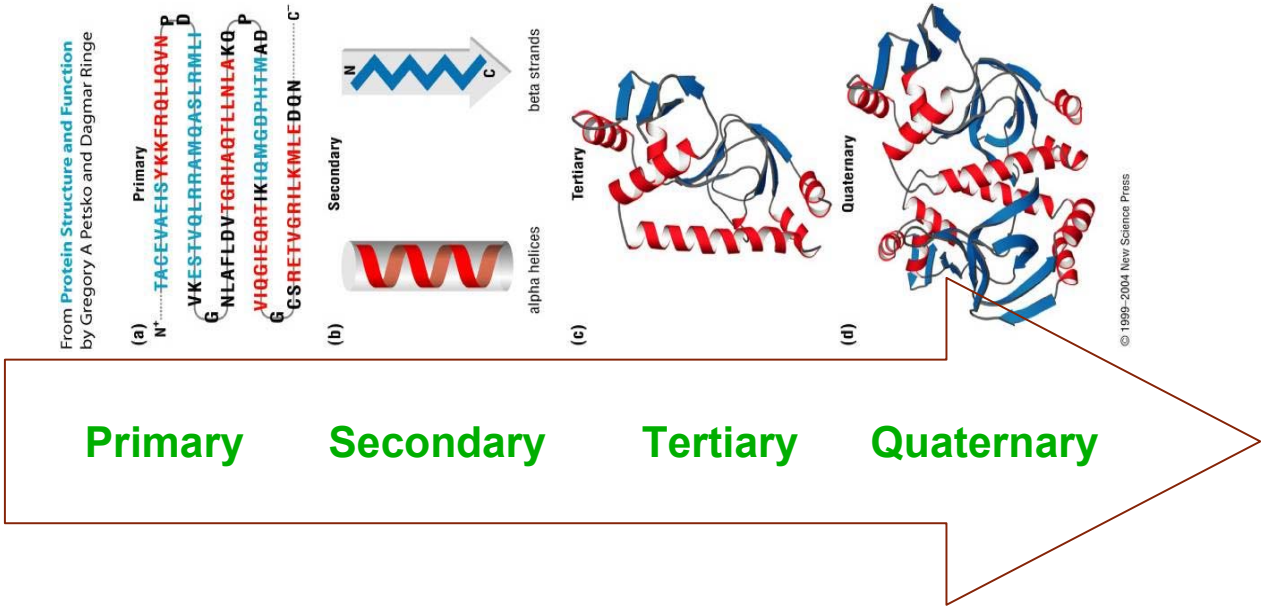
Biopharmaceuticals are structurally more diverse

- Chemical pharmaceutical
- ❑ Simple structure of elements



Aspirin = $C_9H_8O_4$

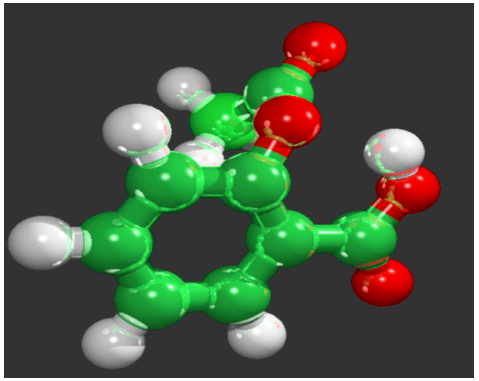
- Biopharmaceutical
- ❑ Multiple levels of structural complexity



Differences between biopharmaceuticals and synthetic chemicals: size and complexity

- Biosimilars try to copy large biopharmaceuticals

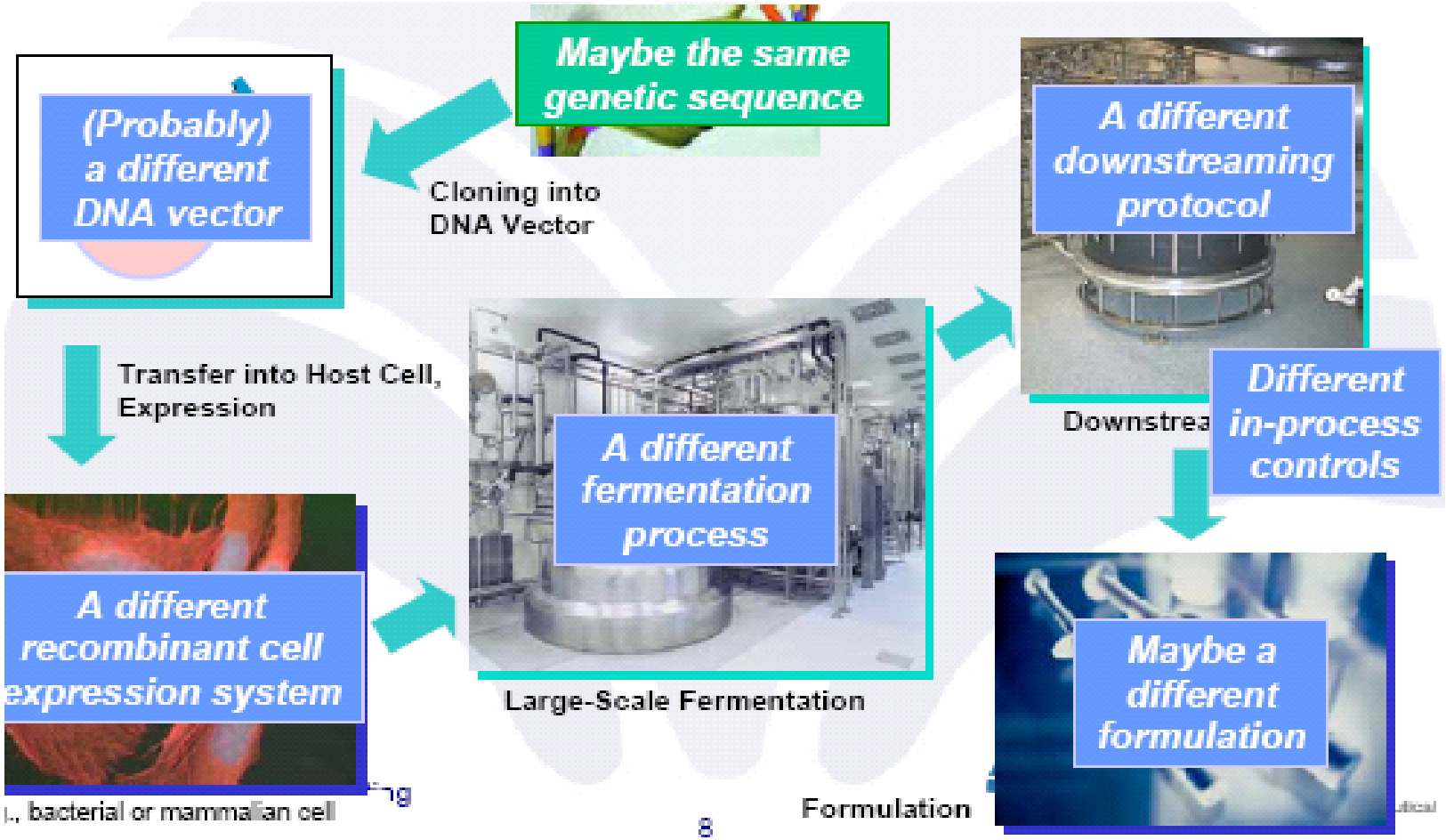
❑ These are >2 logs larger than traditional chemical products, and much more complex



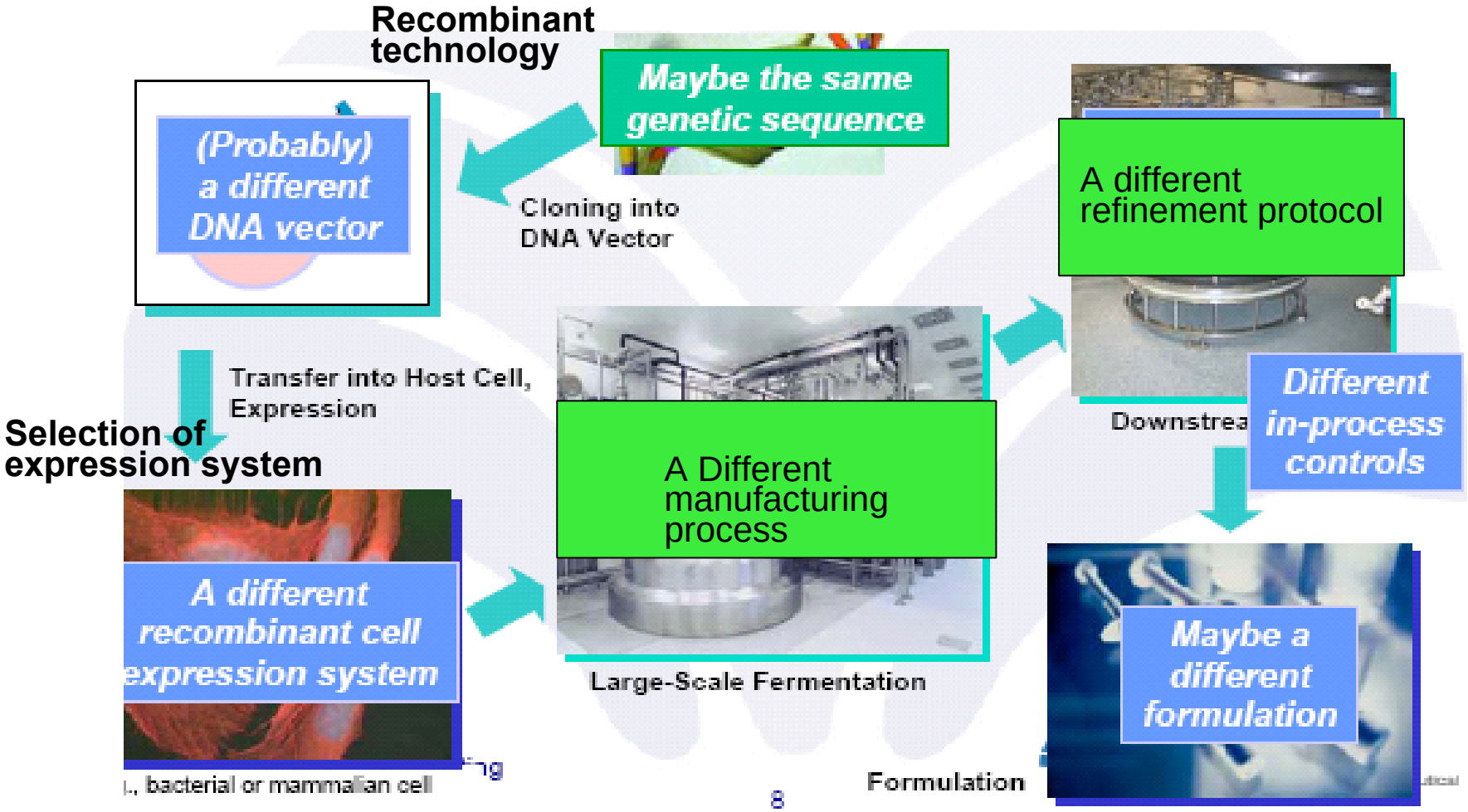
Chemical
Pharmaceutical
Aspirin
(180 daltons)

Biopharmaceutical
G-CSF
(19 600 daltons)

Biosimilars Manufacturers: Different Process→Different Product



Biosimilars Manufacturers: Different Process→Different Product



Biosimilars:Reinventing the Whole Process

	Technical Development	Clinical Development	Drug Product
Originator			
Biosimilars Manufacturer	No access to historical data base No assessment of similarity possible	Limited access to historical database Case-by-case: clinical development can be shortened	Comparison at the level of final product (limited only to drug substance)

IDENTICAL

- The product attributes are the same as those of the comparator drug

SIMILAR

- The product attributes are similar enough to estabilish the same safety and efficacy as the same comparator drug

“Biogenerics” Cannot Exist

Pictures taken from:
http://savingsandclone.com/news/press_room.html

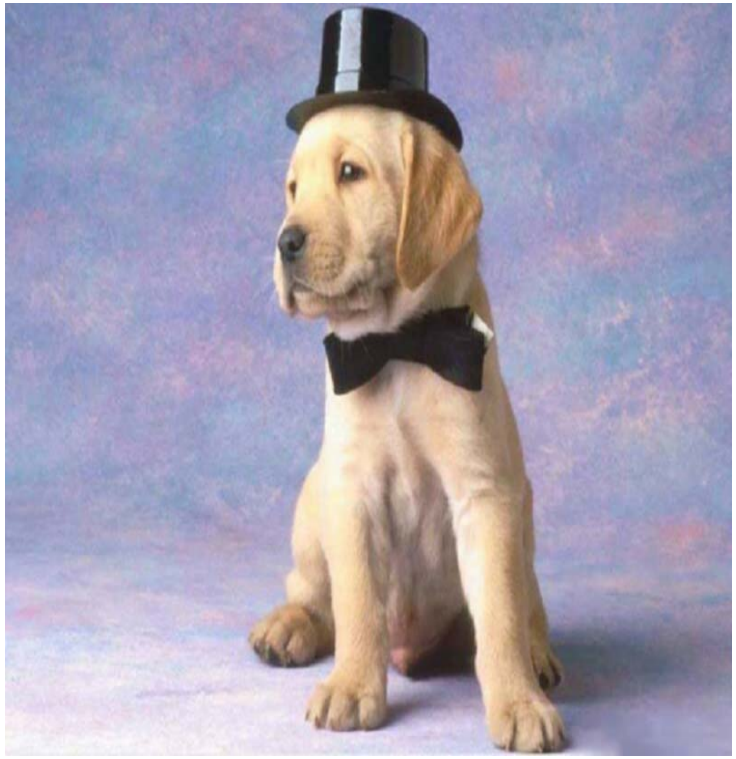
S.Koszlowski (2005) FDA/DIA Scientific Workshop on Follow-on Protein Pharmaceuticals

How similar is similar enough?

How different is too different?

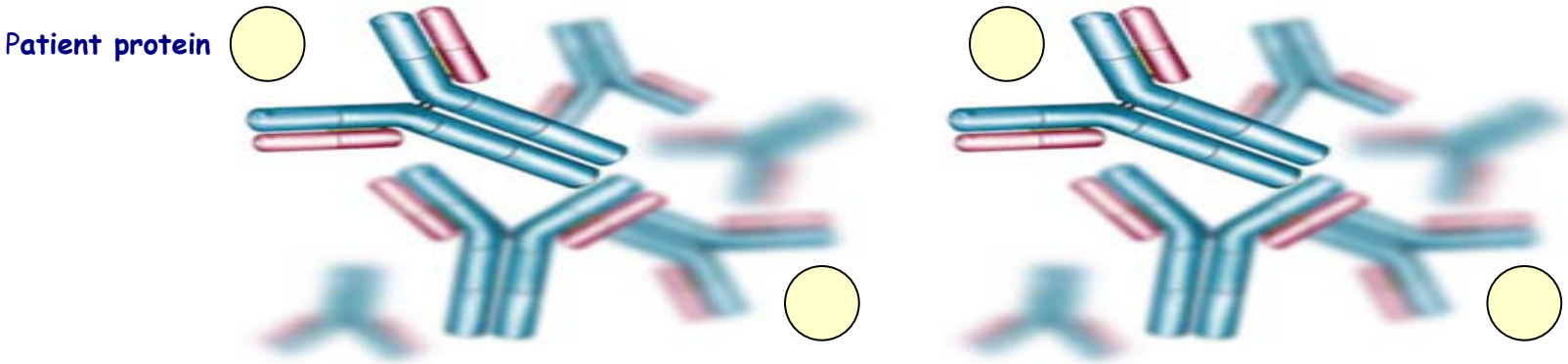
What are the clinical consequences of differences?

What Are The Consequences of differences in the Final Product?



Immunogenicity is the main Safety Issue

- Most biopharmaceuticals induce antibodies
- Immunogenicity can only be revealed through clinical trials
- Antibodies can impair biological activity of the drug and the endogenous protein

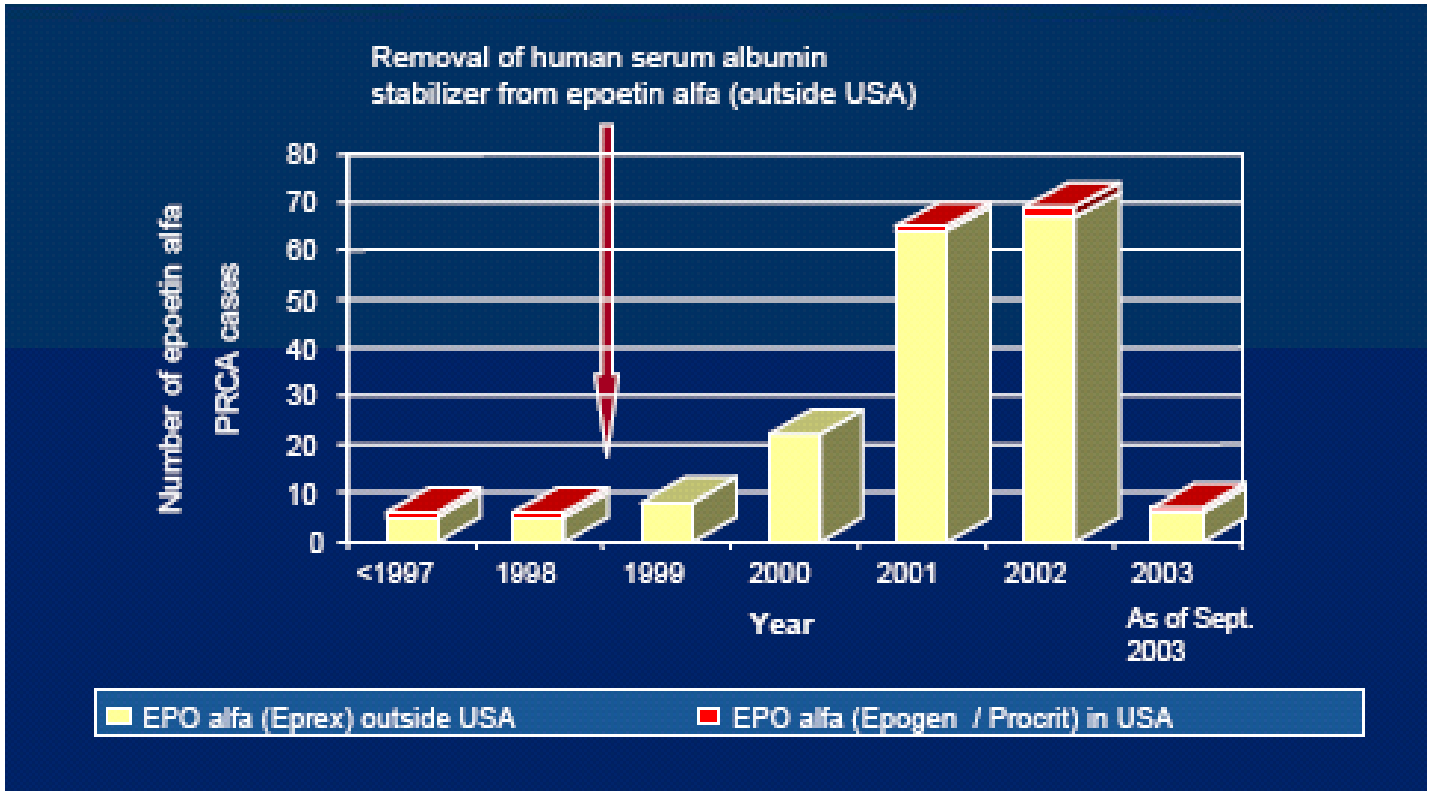


Consequences of Antibodies

- **Loss of efficacy**
  - Insulin
  - Streptokinase
  - Staphylokinase
  - ADA
  - Salmon calcitonin
  - Factor VIII
  - Interferon alpha 2
  - Interferon beta
  - IL-2
  - GnRH
  - TNFR55/IgG1
  - Denileukin diftitox
  - HCG
  - GM-CSF/IL3
- **Enhancement of efficacy**
  - Growth hormone
- **Neutralization of native protein**
  - MDGF
  - EPO
- **General immune effects**
  - Allergy
  - Anaphylaxis
  - Serum sickness, etc.

Biopharmaceutical Formulation: Effect on Immunogenicity

One change in the formulation of an established biopharmaceutical led to unpredicted immunogenicity



http://www.jnj.com/news/jnj_news/1021024_095632.htm. Accessed December 15, 2003.

Immunogenicity is Unpredictable

- There are no available tests or analytical techniques that can prove that two biological products are identical

- There is no means of predicting the immunogenicity of a biological product, aside from rigorous clinical testing

Key Considerations for the Patient

- **The amount of clinical data is critical**
  - To compare with originator product
  - To evaluate potential risks
- **Risk management plans**
  - Should be part of approval process
  - Should include post-authorisation commitments (e.g. clinical trials or patient registries)
- **No experience with Biosimilars**
  - Difficult to assess if extrapolation of indication is possible without additional clinical studies.

Summary

- **Biosimilars are not generics**
  - Biopharmaceuticals are complex→ Identical copies impossible to make
- **Biosimilars must provide full pre-clinical and clinical data**
  - For similarity and comparability testing
- **Primary concerns: quality, efficacy, safety**
- **Small changes in manufacturing make different products**
  - Different process → Different product
- **Immunogenicity: the most important safety issue**
  - Immunogenicity: related to product quality

And so far, similar, yet not the same!