Lokalisering av din kliniska prövning

“Biopharmaceuticals”

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SwedenBIO Clinical Trials Day

2 oktober 2008

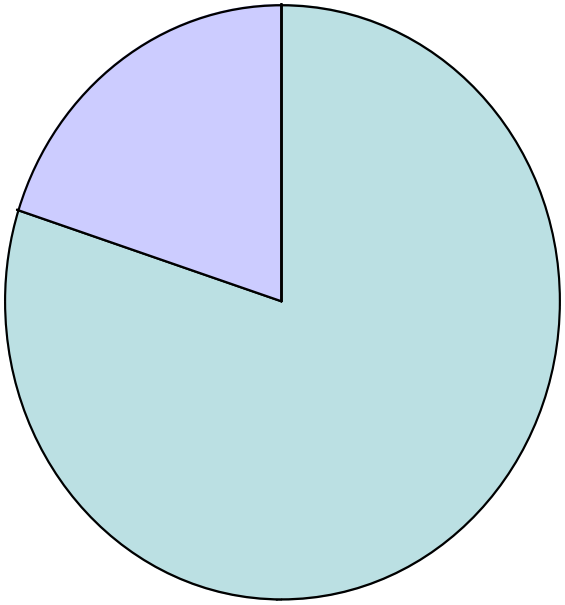
Presentation Outline

- Strategy for Biopharmaceuticals
- Risk factors
  - Transition from non-clinical to clinical trials
  - Immunogenicity
  - Biosimilars

The Biotech Industry

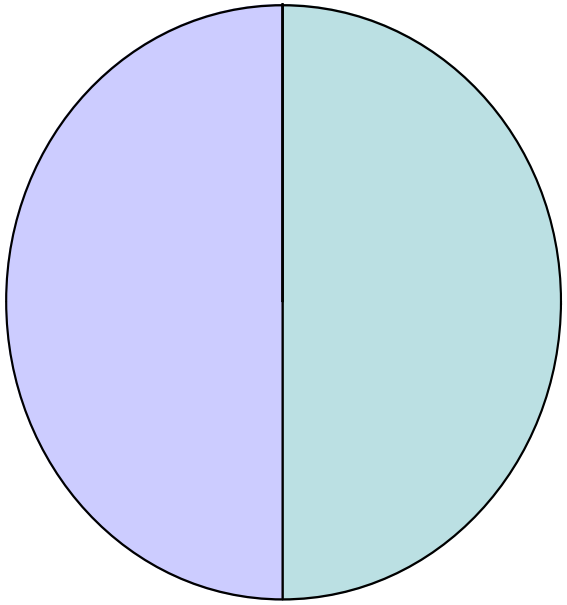
Products on the Market

Biotech 20%



Products in Development

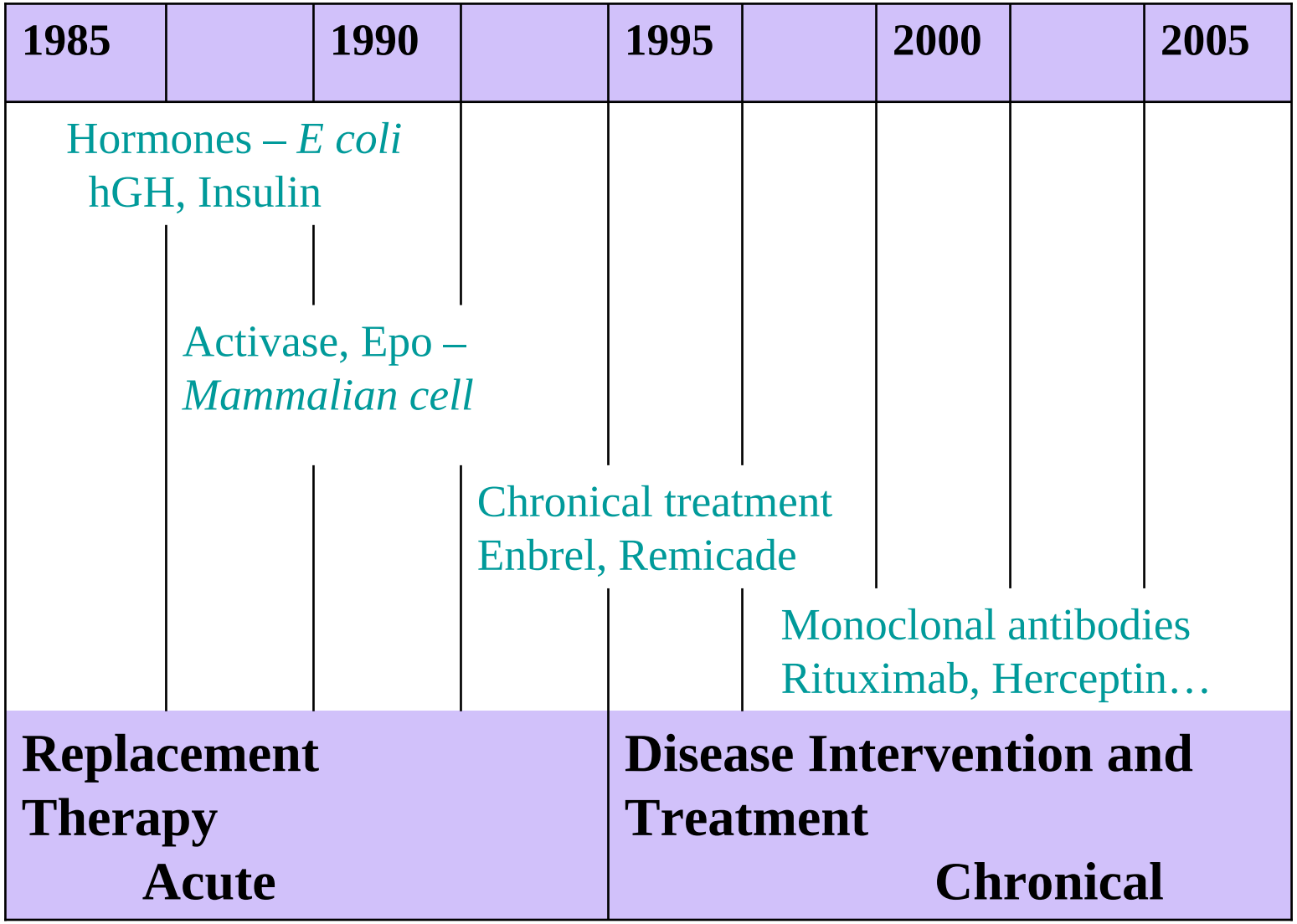
Biotech 50%



Biotech Products in Development

AIDS/ HIV infections etc	22
Autoimmune disorders	44
Blood disorders	10
Cancer and related conditions	210
Cardiovascular diseases	22
Diabetes and related conditions	15
Digestive disorders	14
Eye conditions	6
Genetic disorders	9
Growth disorders	4
Infectious diseases	50
Neurologic disorders	17
Respiratory disorders	13
Skin disorders	7
Transplantation	4
Other	18

Evolution of Protein Therapeutics



Example of Design: tPA to TNK

Changes:
-T103N
-N117Q
-KHRR296-299AAAA

Result of product redesign:
-Biological activity
the same
-Prolonged T1/2
-Increased specificity
for fibrin

Transition from non-clinical to clinical studies

- TGN1412 - TeGenero
  - Protein type: Monoclonal antibody (IgG4)
  - Indication: B-cell chronic lymphocytic leukemia
  - Non-clinical: “Safe”
  - Phase 1 : 8 volunteers (6/2)
    - 1/500 of safe dose in animals
  - Serious adverse Event:
    - Systemic Inflammatory Response/ CytokineReleaseSyndrome

Investigation of TGN1412

- No dosing error
- No formulation issue
- No contamination
- An unpredicted biological effect NOT seen in the adequate non-clinical studies

Recommendation based on TGN1412

- Special considerations in the Transition between non-clinical and first in man (FIM) phase 1
  - Biologic with novel mechanism of action
  - New agents with a highly species-specific action
  - Drugs towards the immune system targets

Immunogenicity

- Most biopharmaceuticals induce antibodies
- The immune system can detect alterations in products missed by analytical methods
- Immunogenicity of biopharmaceuticals may have serious clinical consequences
- Two mechanisms
  - Reaction to foreign proteins
  - Breakdown of immune tolerance

Different potential for immunogenic impurities

Eli Lilly & Co:

Expression system: *E. Coli*

Expressed molecule:

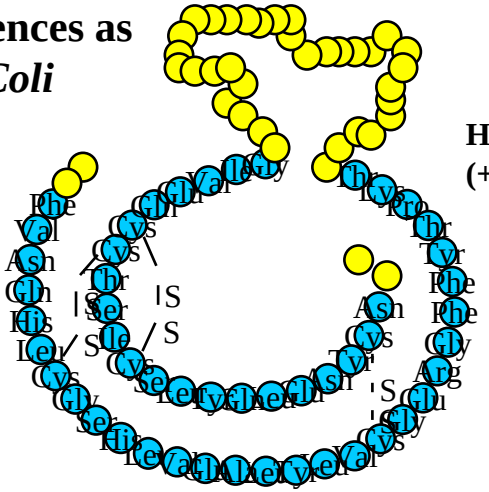
- **Pro-Insulin (35 AA bridge)**
- **+ Leader sequence**
- **+ other sequences as needed in *E. Coli***

Novo Nordisk:

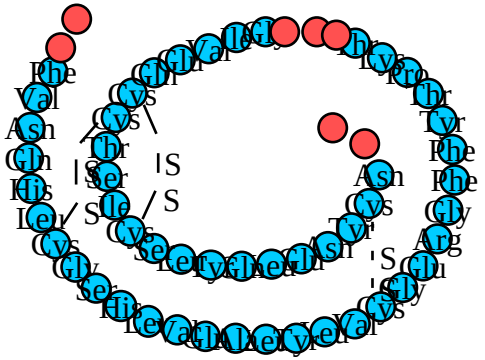
Expression system: *S. Cerevisiae*

Expressed molecule:

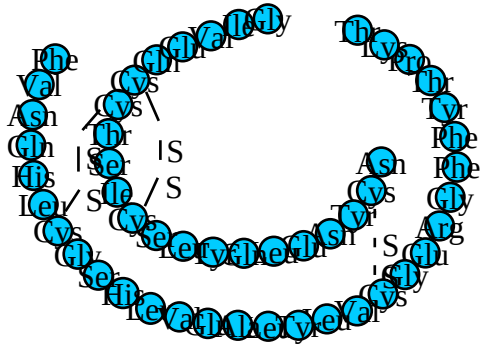
- **Insulin precursor (3 AA bridge)**
- **+ Leader sequence**
- **+ other sequences as needed in *S. Cerevisiae***

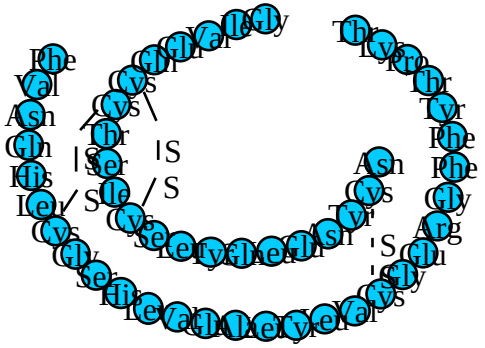


Human Proinsulin (+ other sequences)



Human Insulin Precursor (+ other sequences)





Human Insulin

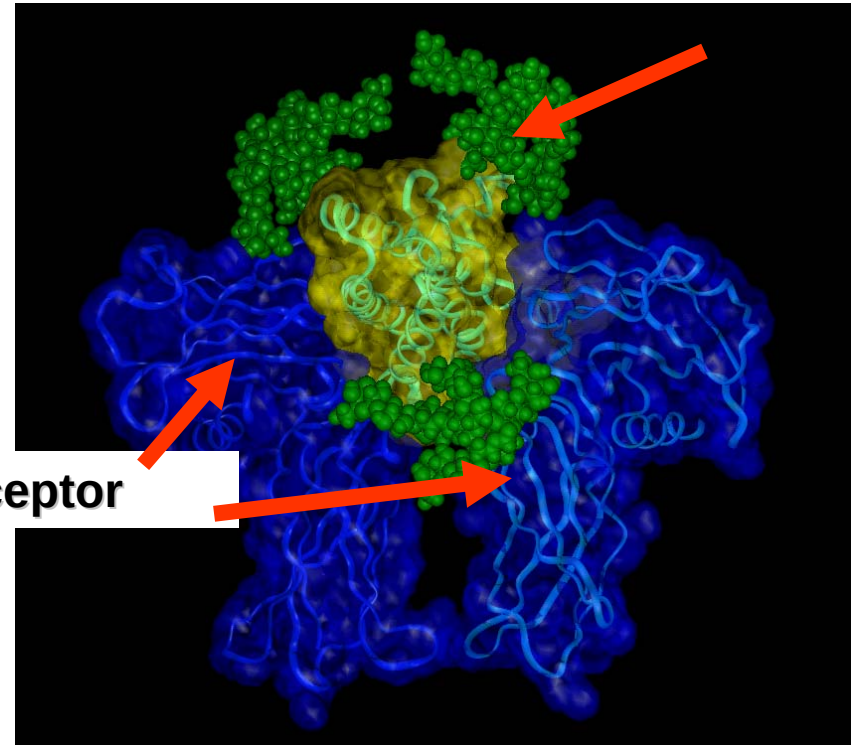
Consequences of formation of antibodies

- Loss of efficacy
  - FVIII, Interferon, Insulin, G-CSF/IL3…
- Enhancement of efficacy
  - Growth hormone
- Neutralization of native protein
  - MDGF, EPO…
- General immune effects
  - Allergy, Anaphylaxis, etc

Other factors influencing immunogenicity

- Route of administration
  - S.c.>i.m.>i.v.>local
- Type of disease
- Genetic background of patients
  - MHC?
  - Hemophilia
- Unknown factors

Case Study: Erythropoietin



Adapted from: Elliott et al. 2003
Nature Biotechnology 21: 414-421.

Several innovator products
Multiple copies in some regions of world

Clinical use:

- Correction or prevention of anemia
- Renal disease
- Chemotherapy induced anemia
- Pre-donation
- Pre-sugical
- Pediatric

EPO-induced PRCA

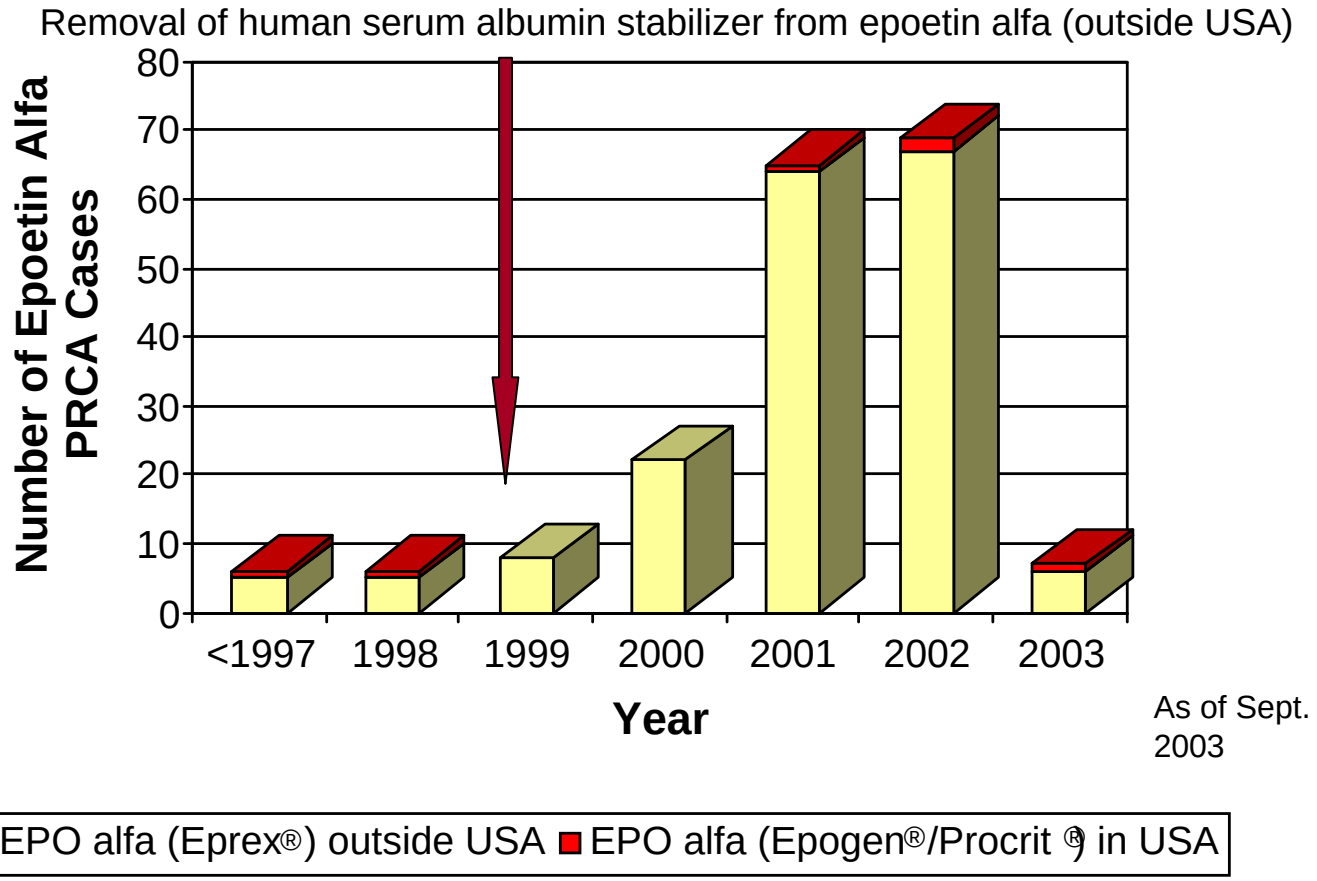
The New England Journal of Medicine

VOLUME 346 FEBRUARY 14, 2002 NUMBER 7

PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

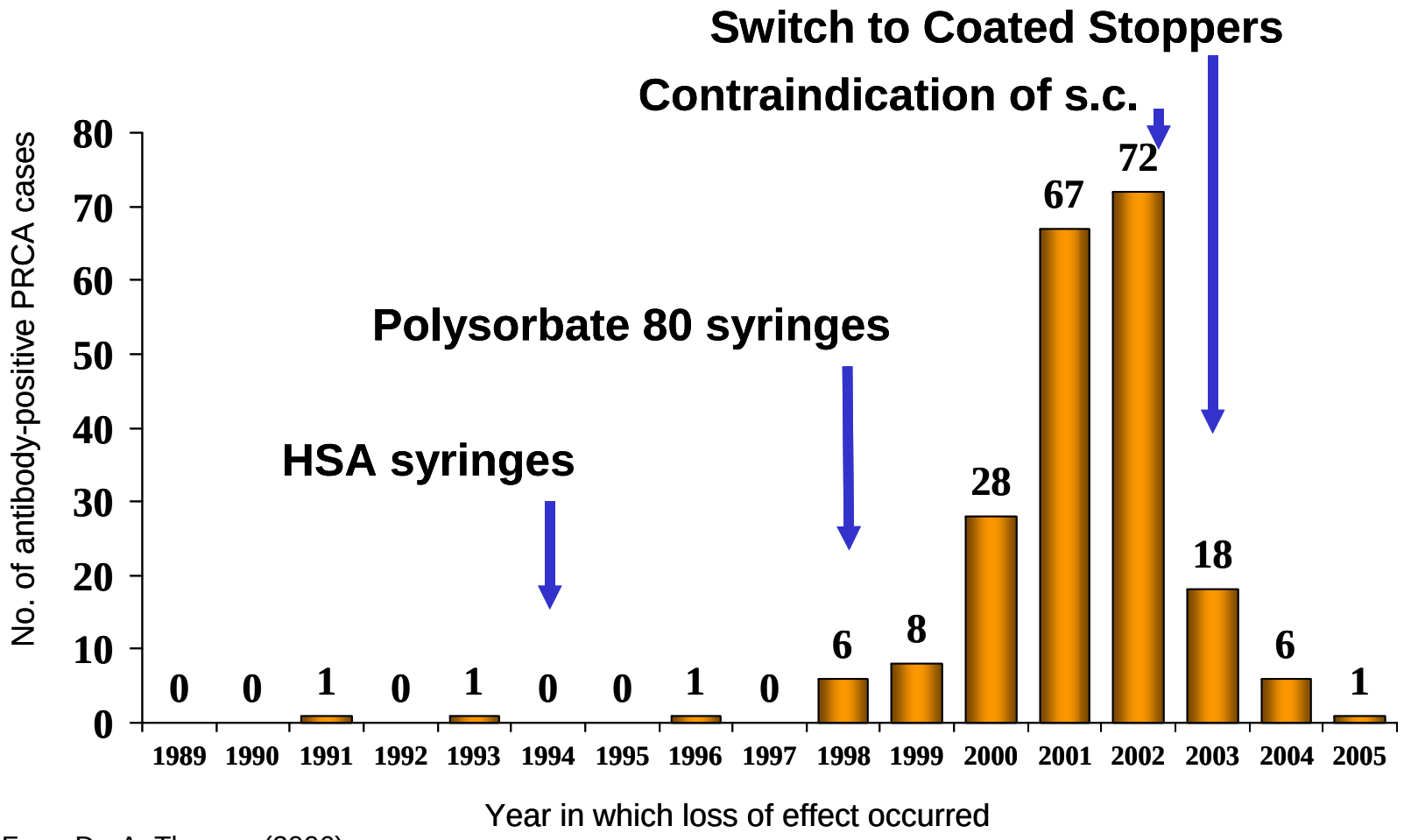
NICOLE CASADEVALL, M.D., JOELLE NATAF, M.D., BÉATRICE VIRON, M.D., AMIR KOLTA, M.D., JEAN-JACQUES KILADJIAN, M.D., PHILIPPE MARTIN-DUPONT, M.D., PATRICK MICHAUD, M.D., THOMAS PAPO, M.D., VALÉRIE UGO, M.D., IRÈNE TEYSSANDIER, B.S., BRUNO VARET, M.D., AND PATRICK MAYEUX, PH.D.

Epoetin Alfa PRCA Cases - Neutralizing of native protein



Johnson & Johnson Pharmaceutical Research & Development LLC. Summary of PRCA case reports. Available at: http://www.jnj.com/news/jnj_news/1021024_095632.htm. Accessed December 15, 2003.

Reporting of PRCA Correlates with the 1998 Formulation Change in EPREX



From Dr. A. Thomas (2006)

Factors potentially contributing to the immunogenicity of Eprex®

- Formation of micelles associated with Epo

  (Hermeling et al, 2003)
- Tween 80-epo interaction

  (Bruce Kerwin, 2004)
- Silicon droplets in the prefilled syringes
- Leachates from rubber stoppers
- Mishandling

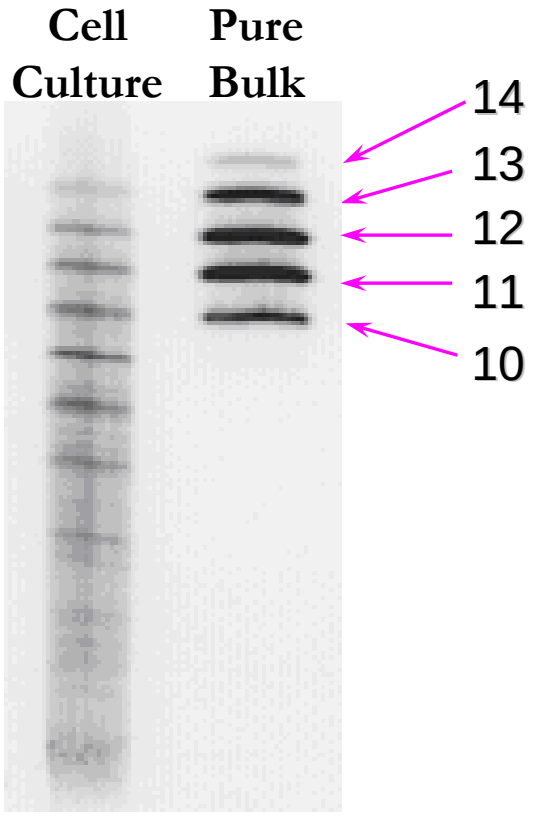
Why is Clinical Testing Necessary?

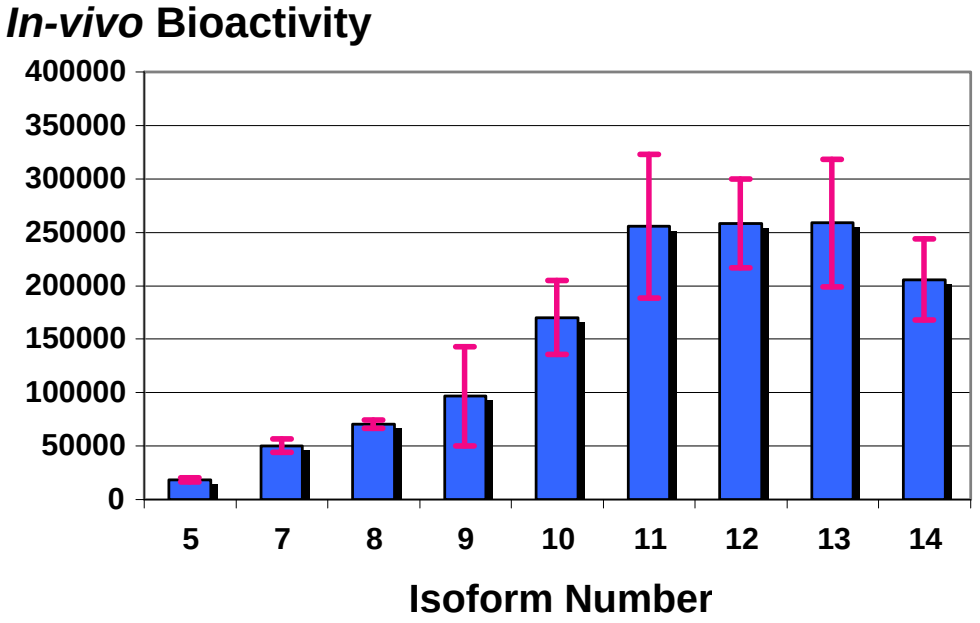
What Clinical Testing is Necessary?

Similar Efficacy and Safety

EPO is a heterogeneous mix of charged forms

Isoelectric Focusing: epoetin alfa product is subfraction of cell culture isoforms

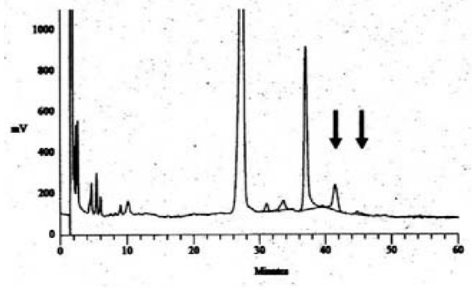


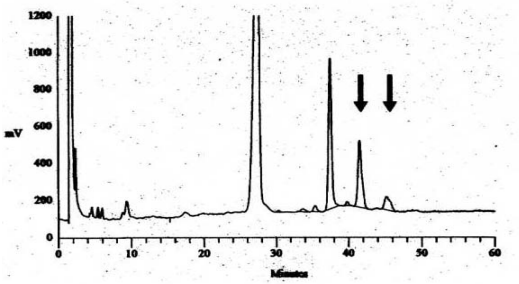


What looks the same may be different

	huEPO - 1	huEPO - 2
IEF pattern and sialic acid content of the two EPOs are very similar		
	isoform 2	isoform 2
… but the biological activity is very different	Sialic acid 14.0	Sialic acid 14.2
	Activity (U/mg) 226,000	**Activity (U/mg) 400,000**

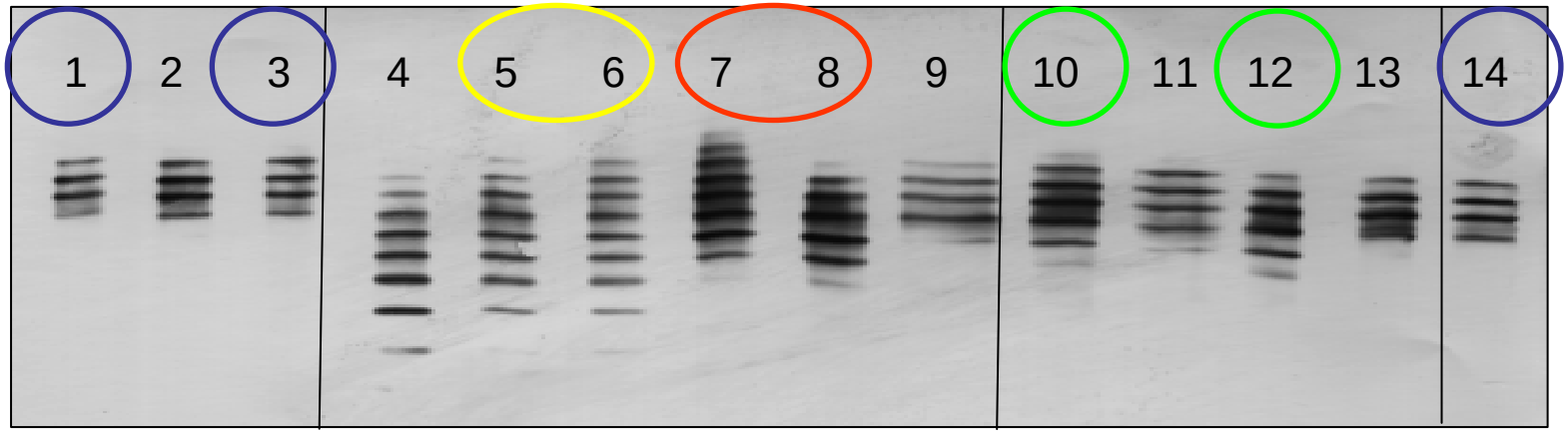
The carbohydrate structures of the two EPO isoforms are different





Adapted from Kresse
(Burg, J. et al. 1998 PCT/EP/98/07876)

Different cell lines and processing affect isoform distribution in the product



Lane number	Company
1	Amgen Epogen, 2K
2	rHuEPO #1, 2K
3	Amgen Epogen, 3K
4	rHuEPO #2, 3K
5	rHuEPO #3, 3K
6	rHuEPO #3, 3K
7	rHuEPO #4, 5K
8	rHuEPO #4, 5K
9	rHuEPO #5, 4K
10	rHuEPO #6, 4K
11	rHuEPO #7, 4K
12	rHuEPO #6, 10K
13	rHuEPO #8, 10K
14	Amgen Epogen, 10K

Isoform distribution of rHuEPO determined by IEF-Western Blots

Regulation – views and definitions

Generic Products

- ”Approval based on abbreviated testing and/or filing scheme”
  - The application is based on knowledge (published or comparative testing) of a previously approved (innovator) product.
    - Biochemical testing
    - Clinical testing – bridging studies, PK trials

Biosimilars

- Challenge is to demonstrate that the quality, safety and efficacy of the biosimilar product is comparable to those of innovator products

Conclusion

- Biopharmaceuticals increased volume of new medicines on the market
- Careful in transition from non-clinical to clinical studies, due to species-specificity
- Immunogenicity can have serious clinical consequences
  - It is not yet possible to fully predict the induction of antibodies
  - The relative immunogenicity of therapeutic proteins can only be evaluated in clinical studies