

# ***Biosimilars***

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American Enterprise Institute  
for Public Policy Research

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*Johnson & Johnson*

***“same” = generics***

***“similar” = biosimilars***  
***(follow-on biologics)***

# Biosimilars

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- Full support for a pathway for the approval of biosimilars in the U.S.
- EMEA (EU FDA): Rigorous, therapy-specific testing standards for biosimilars
- Patient safety is paramount
- “Data protection” essential for innovation

# EU Legislation & Regulations

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- EU legislation:
  - Specifically distinguishes biosimilars from generics in terms of manufacturing and clinical trials
  - Provides 10 – 11 years of data protection as incentive for innovation
- EMEA testing guidelines require:
  - Full chemistry
  - Substantial clinical testing including immunogenicity
  - Post-market safety monitor same as for new product

EMEA engaged in a *public and transparent* process for general and *class-specific guidelines*.

# Committee for Medicinal Products for Human Use (CHMP) Guideline on Similar Biological Medicinal Products (CHMP/437/04)

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“It should be recognised that, **by definition, similar biological medicinal products are not generic medicinal products**, since it could be expected that there may be **subtle differences** between similar biological medicinal products from different manufacturers or compared with reference products, which **may not be fully apparent until greater experience in their use has been established.**

Therefore, in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified.”

# Biological Products Are Vastly Different From Chemically-Based Drugs

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- Biological products are *much larger, more complex* and often not defined by an exact molecular composition.
- The proteins in biological products exhibit an amino acid sequence (*primary* structure), disulfide bonds (*secondary*), and elaborate bending, (*tertiary*) and aggregation (*quaternary*.)
- Many proteins are *glycosylated* (meaning sugar molecules are attached) and have more than one *isoform* (shape).

# Biological Products Are Vastly Different From Chemically-Based Drugs

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- The three-dimensional structure, degree and location of glycosylation, isoform profile, and aggregation profile are all *critical factors* with regard to *efficacy and safety*
- A biological product is a *heterogeneous mixture*
- *Manufacturing differs dramatically*

# Manufacture of Chemically-Based Drugs and Protein Products Differ Significantly

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- Chemically-based drugs are made by *adding and mixing* together known chemicals and reagents using a series of controlled and predictable chemical reactions.

*This is organic chemistry.*

- Therapeutic proteins are made by harvesting the substances *produced and secreted by constructed cells*.

*This is genetic engineering.*

# Production Process

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1. **Create host cell; establish master cell bank**
  - Scientifically, no two cell lines are exactly the same
2. **Fermentation**
  - Grow cells
  - Produce the protein
3. **Purification**
  - Remove impurities & viruses
4. **Filling**
  - Dosage form for patients



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# The New England Journal of Medicine

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## **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.*

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# Immunogenicity

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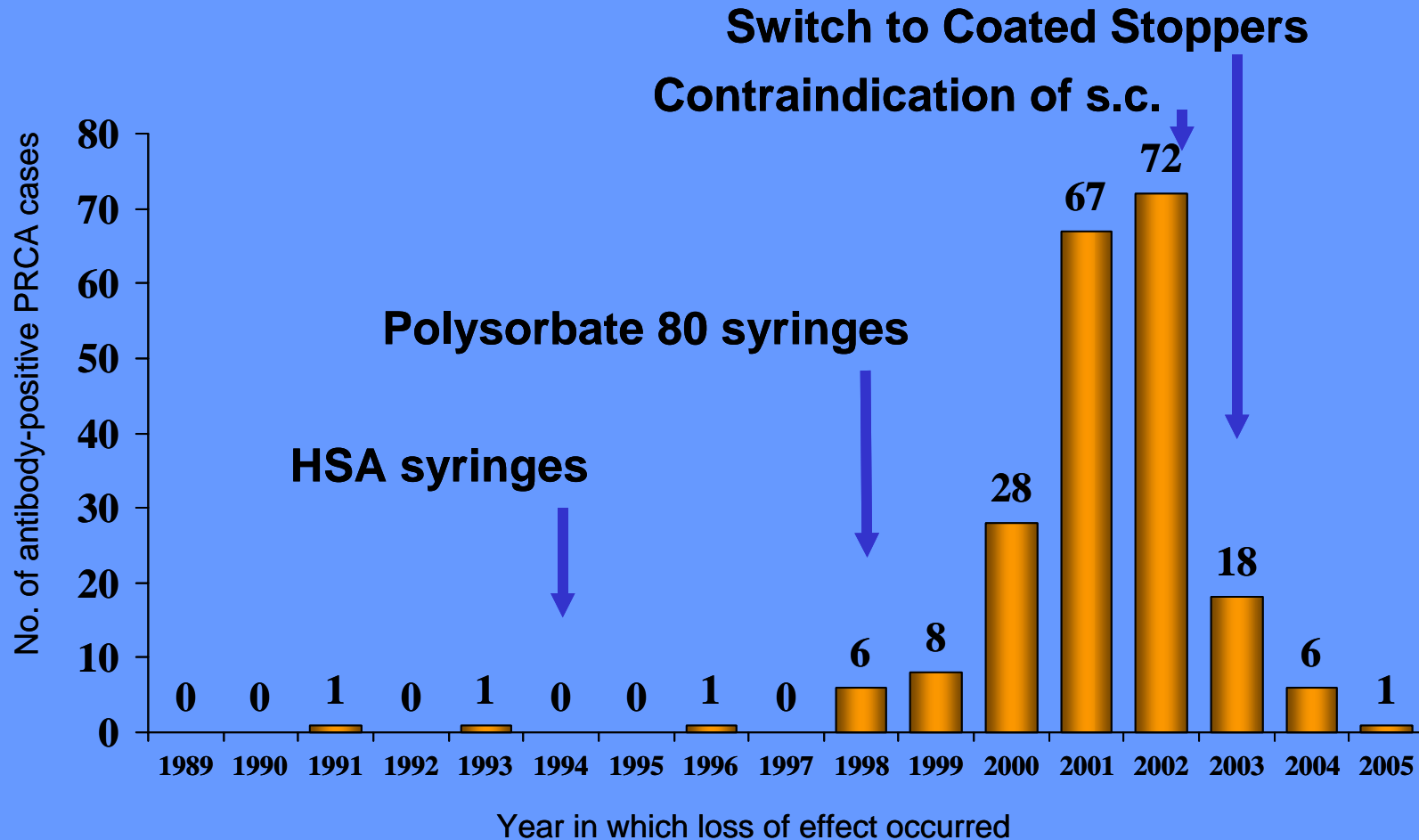
- Therapeutic proteins are inherently immunogenic
- The consequences of immunogenicity range from none to severe, with most serious consequences being:
  - Anaphylaxis ( immune mediated shock)
  - Neutralization of critical endogenous proteins
- Many examples exist of products withdrawn from development, or market related to immunogenicity
- EPREX™ PRCA is just one example

# EPREX™ & Pure Red Cell Aplasia: *Historical Context*

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- EPREX™ (Epoetin alfa) used to treat anaemia in patients with chronic kidney disease
- Significant annual mortality for patients with end-stage renal disease usually related to cardiovascular disease
- Over 2,000,000 patients treated since 1988, thought to be safe and effective

# Reporting of PRCA Correlates with the 1998 Formulation Change in EPREX



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