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EUROPEAN GENERIC MEDICINES ASSOCIATION



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# Erythropoietin

Informal consultation of working group on regulatory  
evaluation of therapeutic biological medicines

WHO 19-20 April 2007, Geneva

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# Content overview

- Erythropoietin structure
- Efficacy
- Safety - immunogenicity
- Conclusion



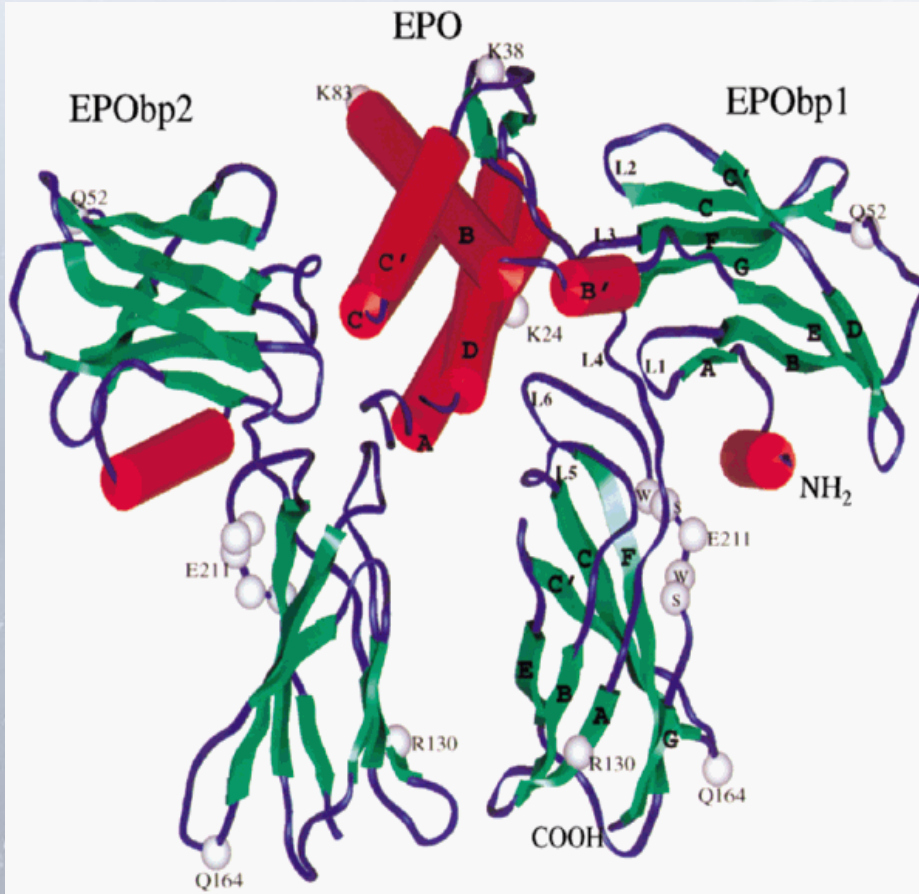
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# Erythropoietin structure

- Recombinant Erythropoietin
- Glycoprotein, 165 aa, aprox. 30 kDa
- Amino acid sequence identical to human sequence
- Peptide component approx. 60%, complex carbohydrate component approx. 40%
- Complex glycan structures of individual molecules glycoisoforms
- Defined mixture of glycovariants having the same amino acid backbone



# Epo - Epo receptor complex



## EPO

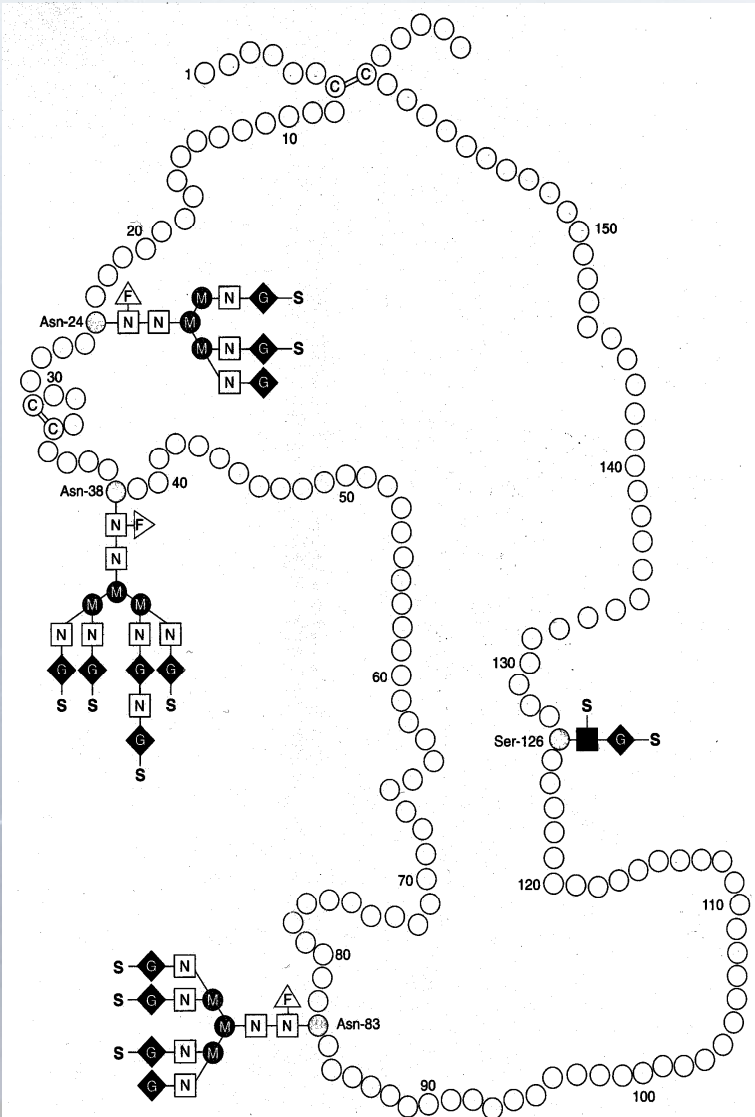
- four-helical bundle (typical cytokine structure)

## EPO receptor

- 508 aa: 24 signal peptide. 226 extracellular. 22 transmembrane, 236 cytoplasmic; glycosylated
- dimer binds EPO
- associated serine kinase
- JAK/STAT signalling pathway



# Erythropoietin structure



- Erythropoietin frequently used as a model protein for glycan characterization
- 4 glycosylation sites
  - 3 N-glycans (complex type)
  - 1 O glycan
- Suitable host: CHO (human-like glycosylation)



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- **The biosimilar development is based on a complete stand alone development of the production process taking all relevant guidelines into account**



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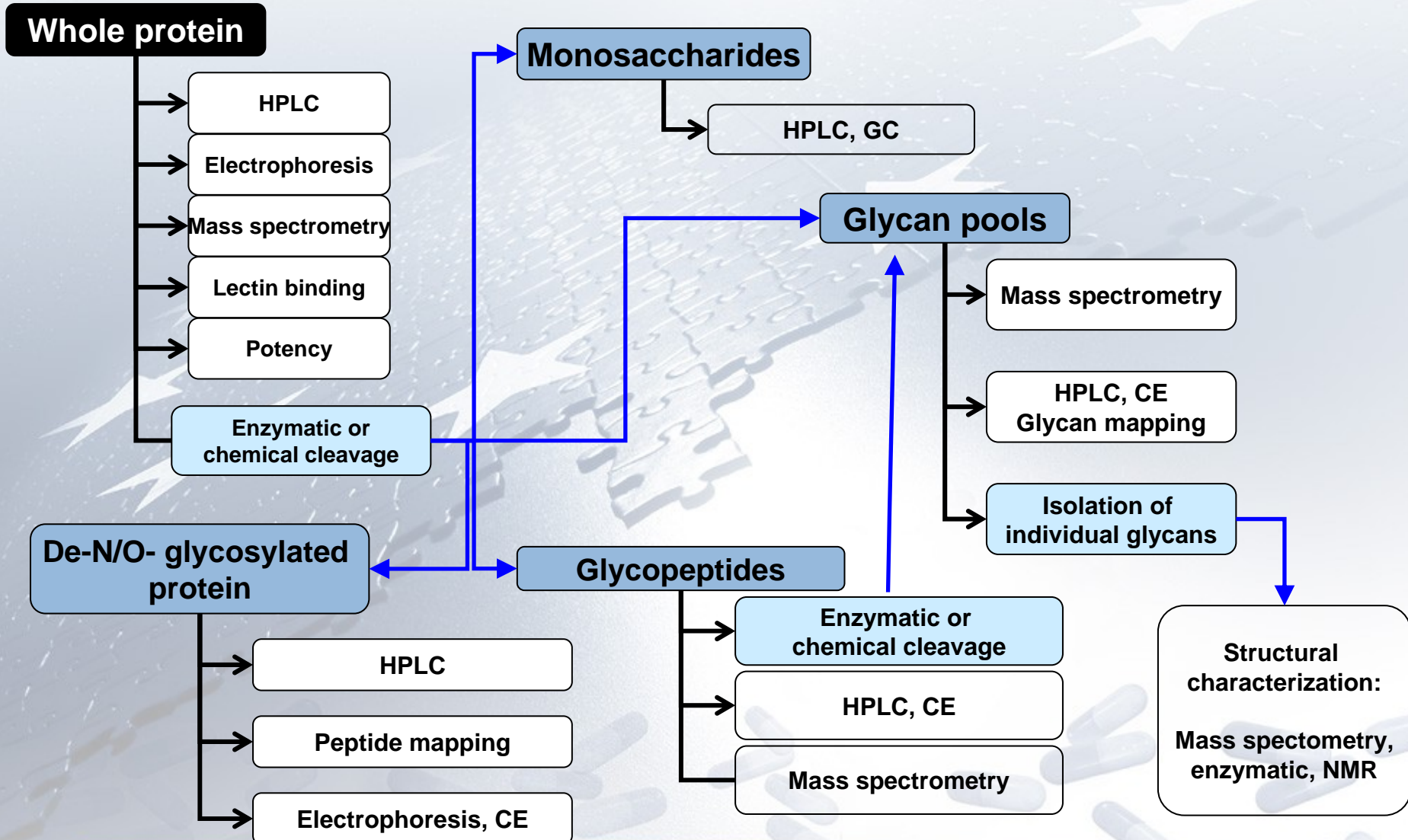
# Efficacy

- **Complete characterization of Erythropoietin biosimilar and reference product**
  - Amino acid backbone
    - Identity and post translational modifications
  - Glycosylation
    - Quantitative composition of the individual glycan structures
    - Structural identification of the single glycans
      - Complete chemical structure
      - Site occupancy
- **Current analytical tools allow complete characterization of Erythropoietin**



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# The analysis of complex glycoproteins requires a combination of multiple analytical methods





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# Efficacy

- **Critical comparability criteria**
  - **Physicochemical comparability**
    - Same amino acid sequence
    - Related substances and impurities
  - **Similar biological activity**
    - Dependent on glycosylation
      - Sialylation
      - Antennarity
- **Any difference with regard to reference product parameters has to be justified**
- **Confirmation by preclinical and clinical data**



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# Safety and immunogenicity

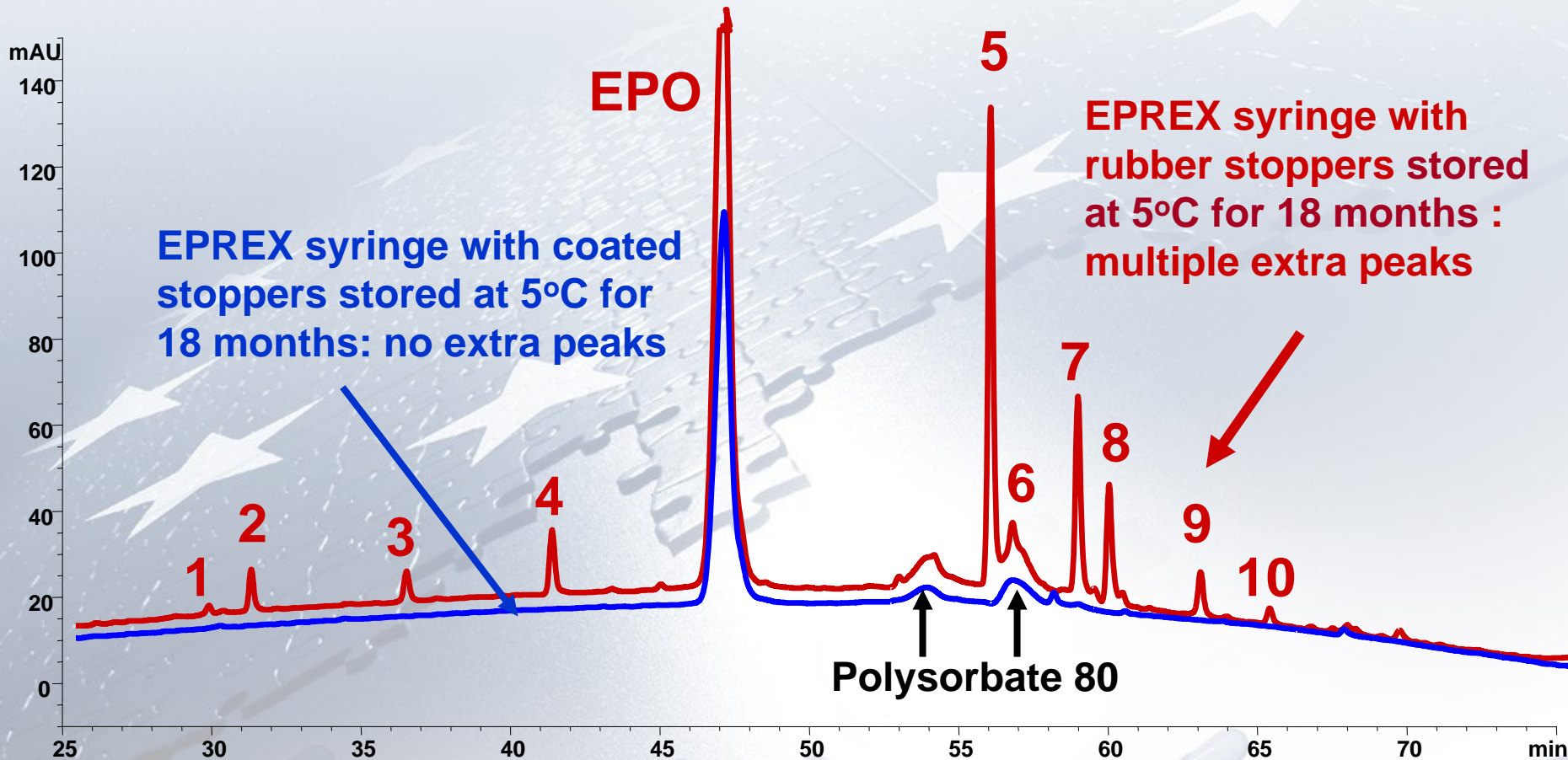
## ■ Drug related safety effects

- Exaggerated pharmacodynamic response may lead to hypertension and thrombosis
- In discussion: possible angiogenic and tumor promoting effects
  - ↳ due to inherent epo activity

## ■ PRCA

- Enhanced development of PRCA related to a formulation change of Eprex<sup>®</sup>
- Most probably due to leachates of the primary packaging material
  - ↳ General quality aspect, which has to be considered in both innovative and biosimilar development

# HPLC of EPREX polysorbate 80 formulations with rubber and FluroTec<sup>®</sup> coated syringe stoppers



- Leachates only occur with uncoated rubber stopper syringes

(Reference: J&J data presented at the FDA Public Workshop, September 14 & 15, 2004)

# Immunogenicity

## ■ PRCA case

- Since PRCA case, leachate data are considered with much higher scrutiny
  - State of the art in primary packaging development has improved significantly
  - Nowadays, a product with such high leachate levels that were seen after the Eprex<sup>®</sup> formulation change will not be released for human use
- ↳ This applies for both innovator and biosimilars

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# Conclusion

- Current analytical technologies allow the complete physicochemical and biological characterization of Erythropoietin required for a biosimilar development
- The biosimilar development of Erythropoietin should
  - Be based on the current state of the art in biotech industry
  - Follow the CHMP guidelines on similar biological medicinal products and the Annex regarding products containing recombinant erythropoietin
- Consequence of Erythropoietin clinical history
  - Improvement of primary packaging material in order to avoid elevated levels of leachates