

PhRMA Perspective on Follow-on Biologics

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**Marie Vodicka, Ph.D.
Science and Regulatory Affairs
mvodicka@phrma.org**

About PhRMA



- **The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the United State's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives.**
- **PhRMA companies are leading the way in the search for new cures.**
- **PhRMA members invested an estimated \$44.5 billion in 2007 in discovering and developing new medicines.**
- **Industry-wide research and investment reached a record \$58.8 billion in 2007.**

Overview



- Biologics have resulted in and will continue to lead to critical medical advances
- U.S. situation for follow-on biologics
- The unique scientific characteristics of biologics must be taken into account in the creation of abbreviated regulatory pathways for approval of follow-on biologics
- An abbreviated approval pathway for follow-on biologics must be science based and ensure continued patient safety and confidence in their medicines

New Medicine Development is Lengthy, Costly, and Risky



- **New medicine development is a lengthy process:** The average development time has increased to between 10 and 15 years.¹
- **The R&D process is very risky:** For every 5,000 to 10,000 compounds tested, just 5 will make it to clinical trials and, of those, only 1 will eventually receive FDA approval.
- **R&D expenditures for each new biologic averaged \$1.24 billion in 2006.**¹
- **Only 2 in 10 approved medicines bring in enough revenue to recoup the average cost of development.**
- **Individual company returns reflect the high risk and long lead times inherent in drug discovery and development.**

“

*It is virtually impossible to find other historical examples [outside of the biotech sector], at least at the industry level, for which such a large fraction of new entrants can be expected to endure such prolonged periods of losses and for which the vast majority may never become viable economic entities.*² ”

— Gary Pisano, Harvard Business School

Sources: ¹DiMasi, JA and Grabowski, HG. “The Cost of Biopharmaceutical R&D: Is Biotech Different?” *Managerial and Decision Economics* 469-79 (Jun. 2007); PhRMA. “Drug Discovery and Development: Understanding the R&D Process.” (2007). ²Pisano, GP. “Science Business – the Promise, the Reality, and the Future of Biotech.”

The Growing Importance of Biotechnology Medicines

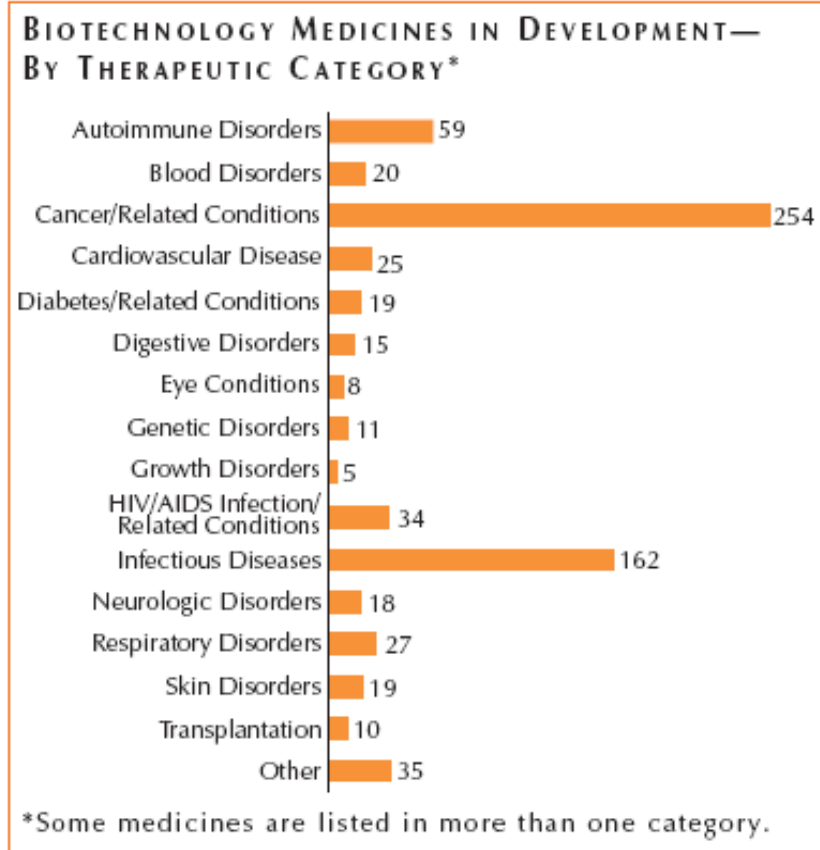


- **Biotechnology medicines have been proven to be safe and effective with an excellent record of patient satisfaction and safety**

- **Biotechnology has produced more than 125 medicines including for some of the most serious and intractable diseases**

- **In 2008, there were 633 biotechnology medicines in development**, including 254 for cancer and related conditions and 162 for various infectious diseases.

- **Reaching a biologic's full therapeutic potential can take time.** New treatment advances are often realized from biologics that have been on the market for some time, but which were not known until additional research was conducted.



There is No Harmonized Worldwide Regulatory Framework for Follow-on Biologics



- **Small molecule generics model is inappropriate**
- **In many regions around the world there either are no regulatory processes or they are very limited**
- **Lack of minimum regulatory standards presents a risk for patients because of the potential issues relating to the quality, efficacy, and safety of follow-on biologics developed and approved without defined requirements**

Science-based FOB pathway



PhRMA thinks that abbreviated regulatory pathways for the approval of follow-on biologics should be science-based, put patients first and promote incentives for innovation.

U.S. Situation



United States



- **A regulatory approval pathway for follow-on biologics in the U.S. requires legislation by Congress.**

FDA Approval Pathways



- **Small molecule drugs approved through *New Drug Application (NDA)***
 - Regulatory framework set out in Food, Drug, and Cosmetic Act (FDCA)
 - FDCA section 505
 - Abbreviated approval pathways exist
- **Biologic drugs licensed through *Biologics License Application (BLA)***
 - Regulatory framework set out in Public Health Services Act (PHSA)
 - PHSA section 351
 - No abbreviated approval pathway

Some “Biologics” Are Approved under FDCA

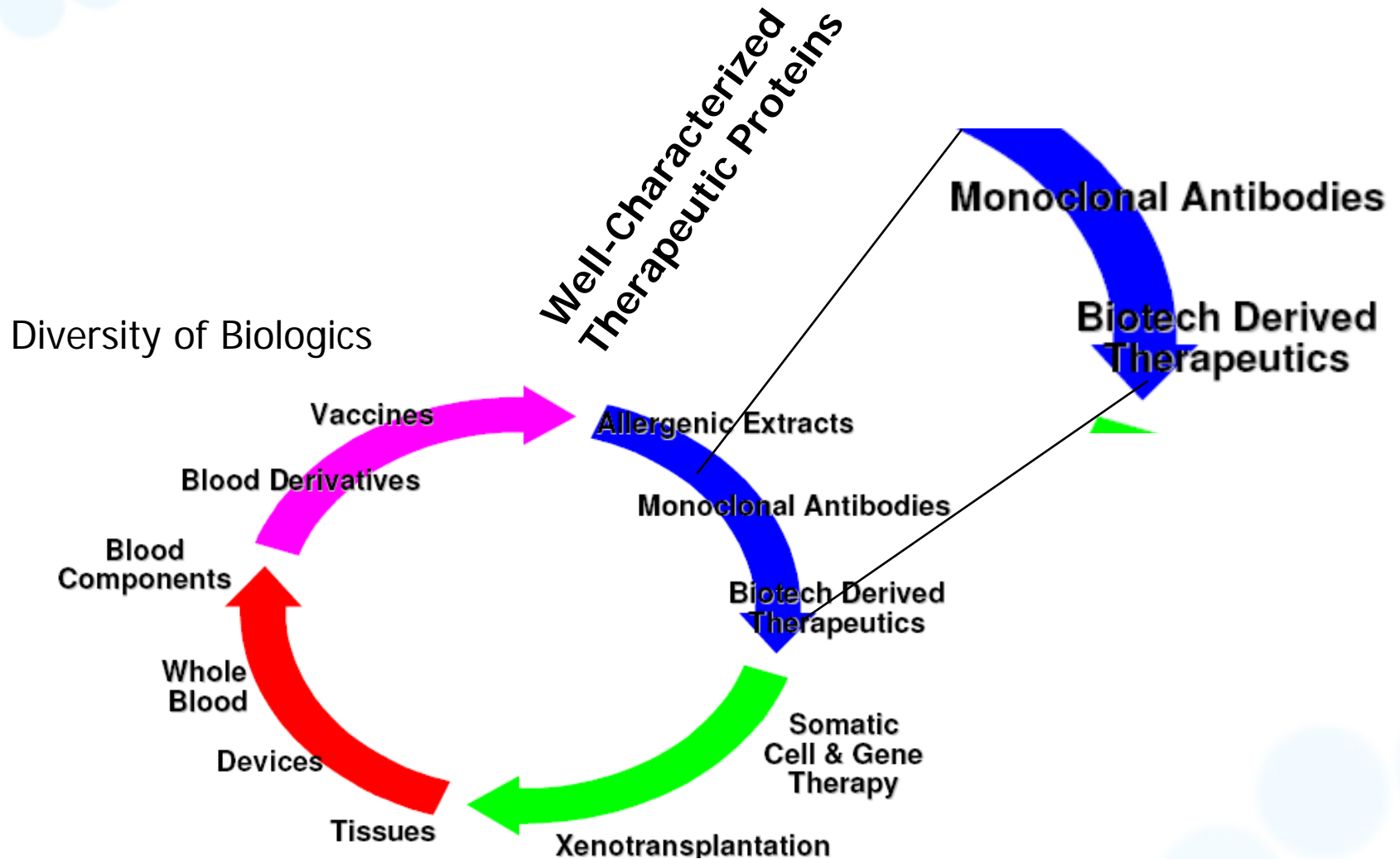


- **For historic reasons, FDA evaluates and approves some products under Section 505 that could meet the definition of biologics**
- **FDA administrative policy, not statutory**
- **Examples include insulin and other hormones**

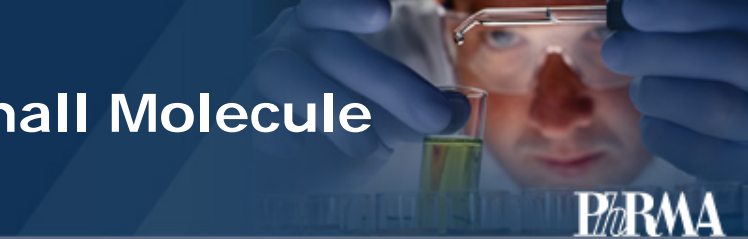
Applying Science & Experience to developing FOB approval pathways



A sub-set of biologics are relevant for follow-on biologics applications: *Well-Characterized Therapeutic Proteins*



Biologics are Different from Small Molecule (Chemical) Drugs



- **Composition, Size, Structure**
 - Larger, more complex, more heterogeneous
- **Manufacturing**
 - Genetic engineering vs. organic chemistry
 - Synthesis by living cells/organisms
- **Clinical Safety**
 - Species specificity limits standard pre-clinical models for safety testing
 - Usually injected
 - Immunogenicity

- **Similar \neq Same**
 - **Everything else follows from this:**
 - Molecular similarity
 - Require Clinical trials
 - Different names
 - No scientific basis currently for automatic substitution/interchangeability

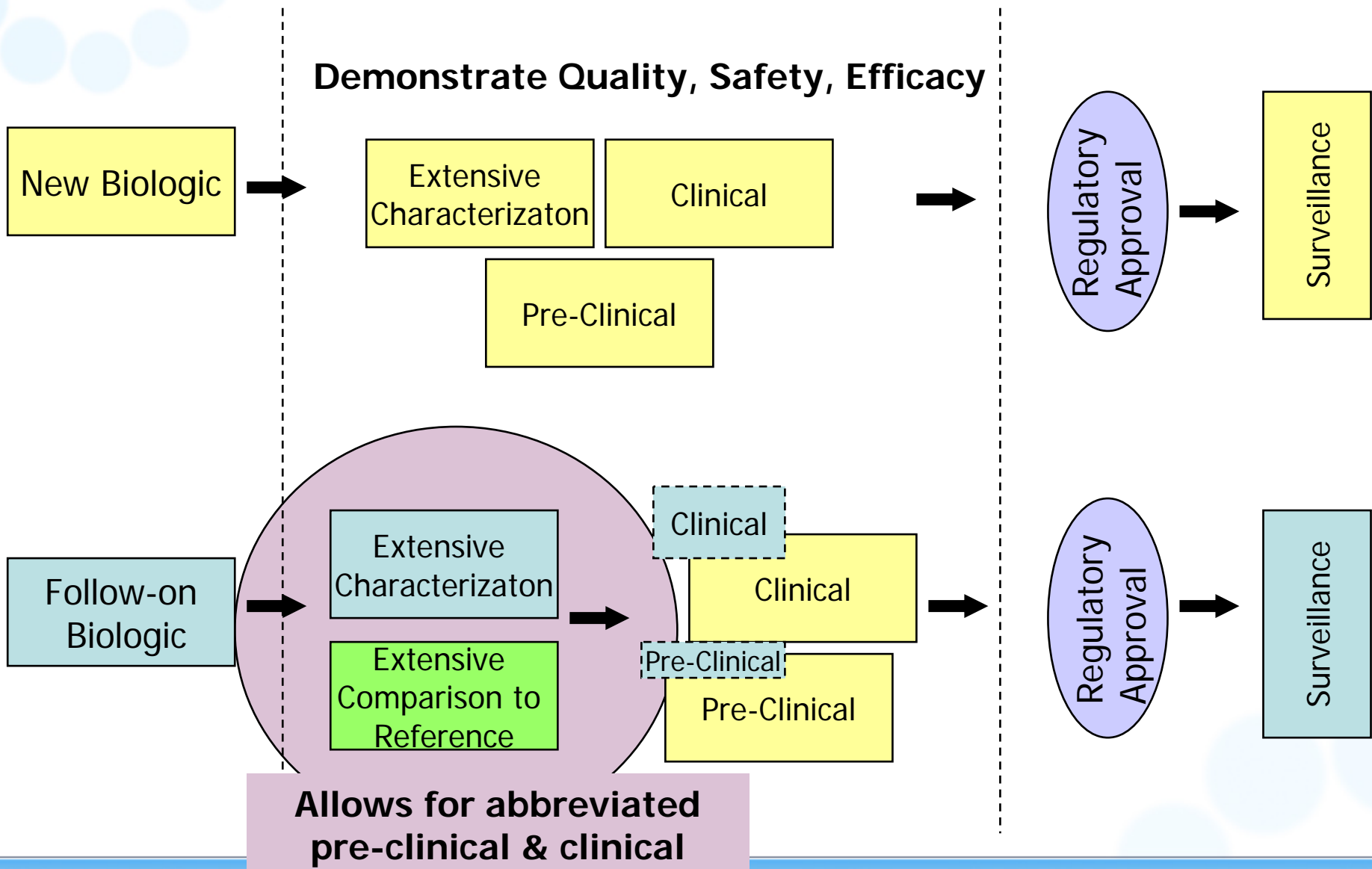
Same, different, similar



- **Generic drug regulatory approval pathway premised on ability to make and show that generic drug is the same as the innovator drug**
- **Biologics from different manufacturers may be shown to be similar, not the same**
- **Therefore you need a different regulatory pathway, with different scientific standards**
- **Follow-on biologics are not generics**
 - The regulatory pathway should reflect this in the rigor of the approval standards.

Follow-on Biologics

Scientific basis for abbreviated pathway



Key concepts for Safe and Effective Follow-on Biologics



1. **Clear regulatory pathway for new product category distinct from small-molecule generics: Follow-on Biologics**

- Open, transparent process with category-specific guidance, including a stepwise approach for products to be covered
- Using reference products that have extensive clinical data and market experience, approved with full data package and review
- Includes a system for distinct naming and labeling (clear prescribing, dispensing and surveillance)

2. **Adequate quality standards**

- Products need to have similar molecular structural properties
- Same quality standards as for innovative products
- Robust comparative physico-chemical and biological characterization to be specified

3. **Adequate pre-clinical and clinical testing requirements**

- Case-by-case approach within the scope of pre-defined non-clinical and clinical requirements, demonstrating safety and efficacy
- Clinical data for each indication unless otherwise scientifically justified
- Appropriate risk management and active pharmacovigilance

4. **Appropriate use**

- Science currently does not support automatic interchangeability/substitution



- **EMA: Similar Biological Medicinal Products**
 - Not “generics”
 - Require demonstration of similarity:
 - Molecular
 - Clinical
 - General, quality, non-clinical, and clinical guidelines
 - Product class specific guidelines
 - Useful regulatory experience gained from EMA experience with biosimilars

Clinical Testing is Necessary for approval of Safe & Effective Follow-on Biologics



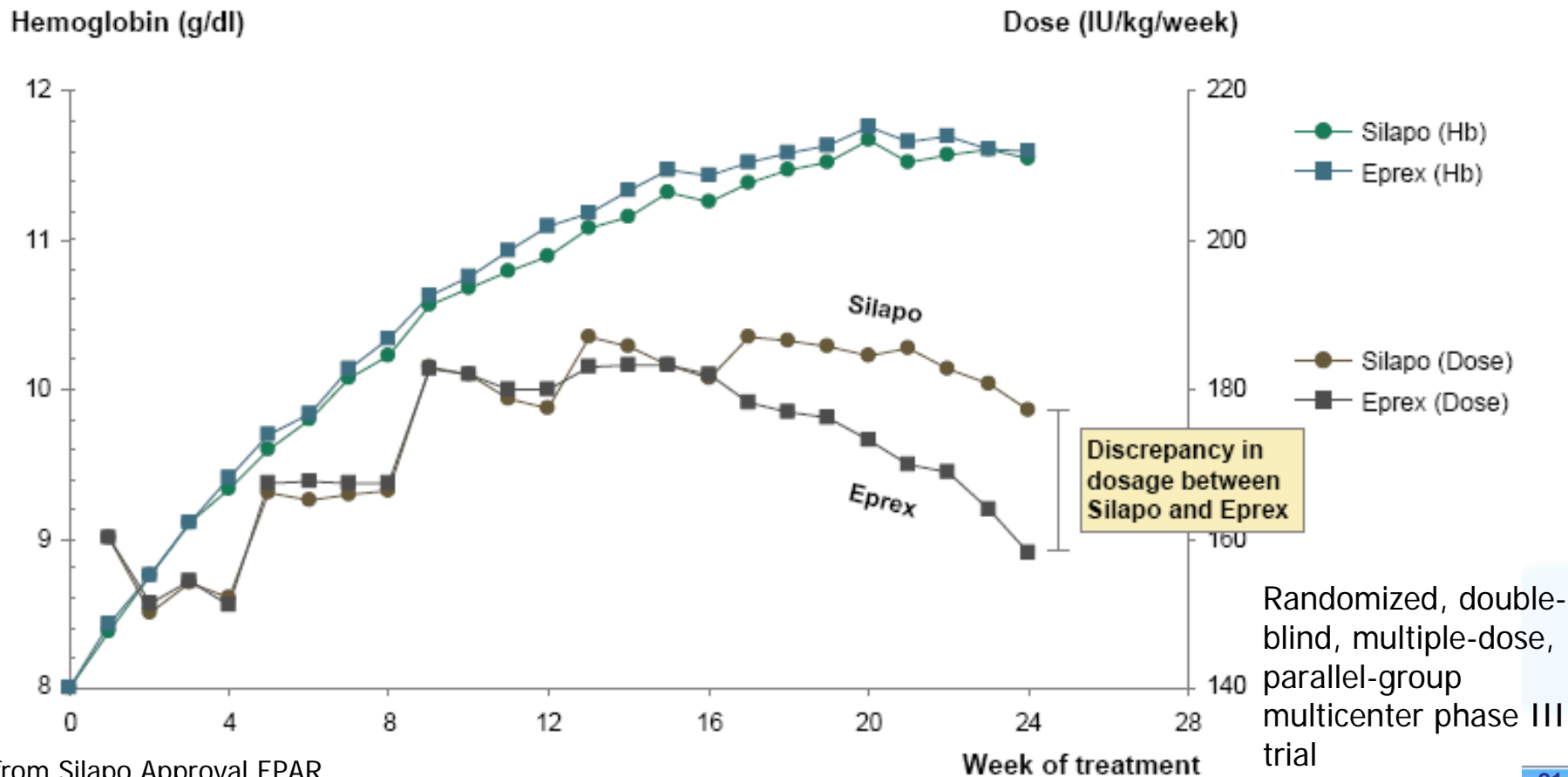
- **Similar Clinical Efficacy**
 - Increased or reduced efficacy could lead to safety problems
- **Similar Clinical Safety**
 - Including Immunogenicity
- **PK/PD studies alone not sufficient**
- **Automatic substitution not appropriate**
- **Distinct names critical for patient safety**
- **Relevant case studies available**

Clinical Data from Silapo (epoetin zeta) EPAR



Different doses to achieve same clinical effect

Hemoglobin levels versus erythropoietin dosage



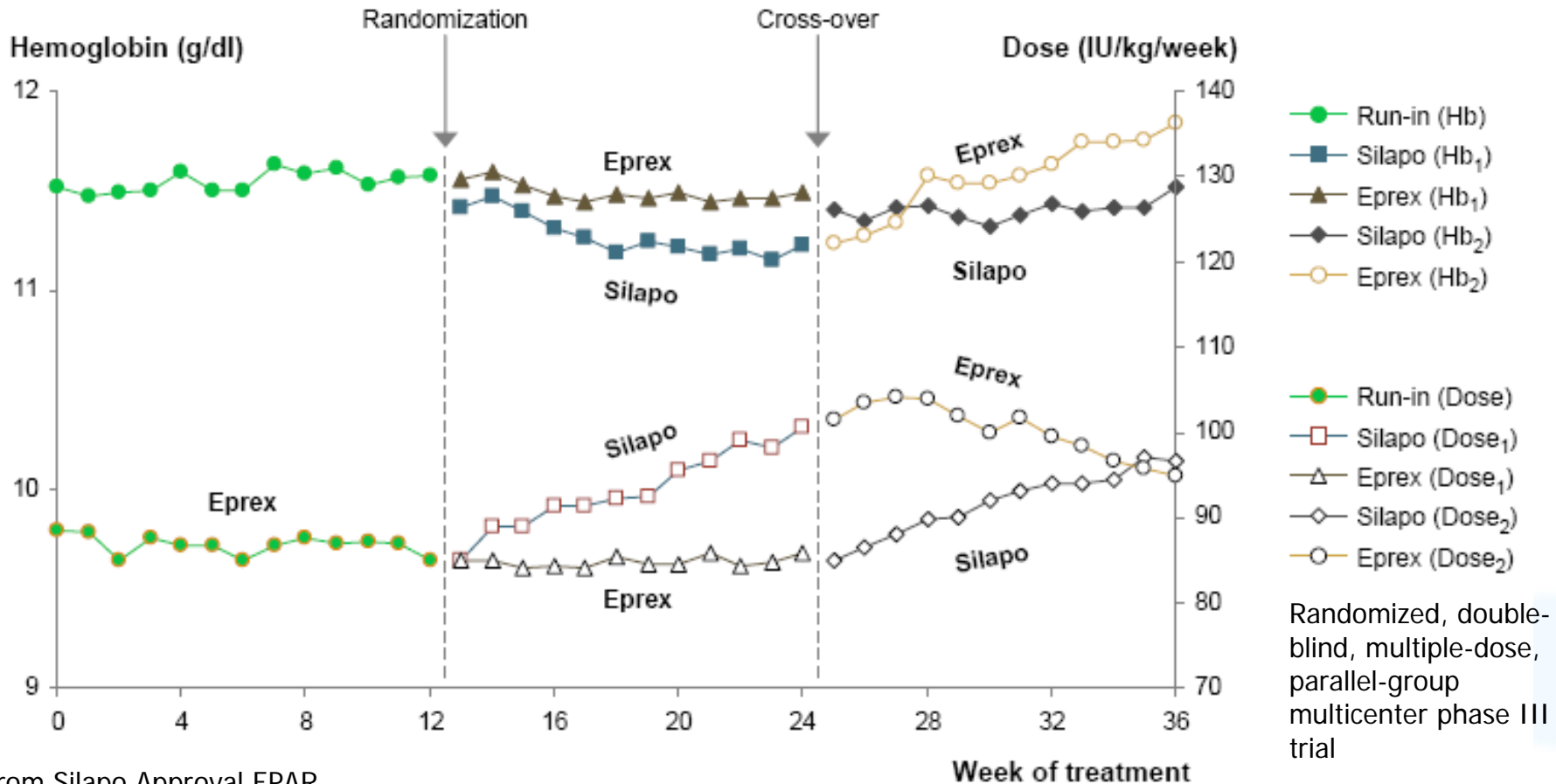
Data from Silapo Approval EPAR

Clinical Data from Silapo (epoetin zeta) EPAR



Different doses to achieve same clinical effect

Hemoglobin levels versus nominal-based epoetin dosage



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