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Development of Biosimilar Drugs, Opportunities and Challenges

Yingfei Wei, Ph.D.

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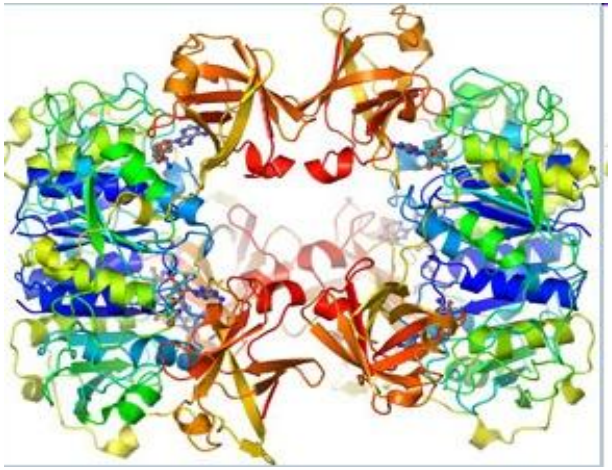
About Biosimilar Drugs

- A “copy” of the patent expired biological drug (protein/ppt/mAb)
- Different from the generic small molecule drugs – much more complicated, never truly be “IDENTICAL”
  - Big size, post-translational modification
  - Heterogeneous isoforms
  - Immunogenicity
  - Complicated manufacture process
  - Injected proscription drug
- Need special regulatory process & guidelines
  - Efficacy & safety – in vitro/in vivo tests
  - Immunogenicity test
  - Post-market surveillance
- Need special legislation
  - Years of exclusivity
  - Interchangeability/automatic substitution



Higher success rate, lower development cost

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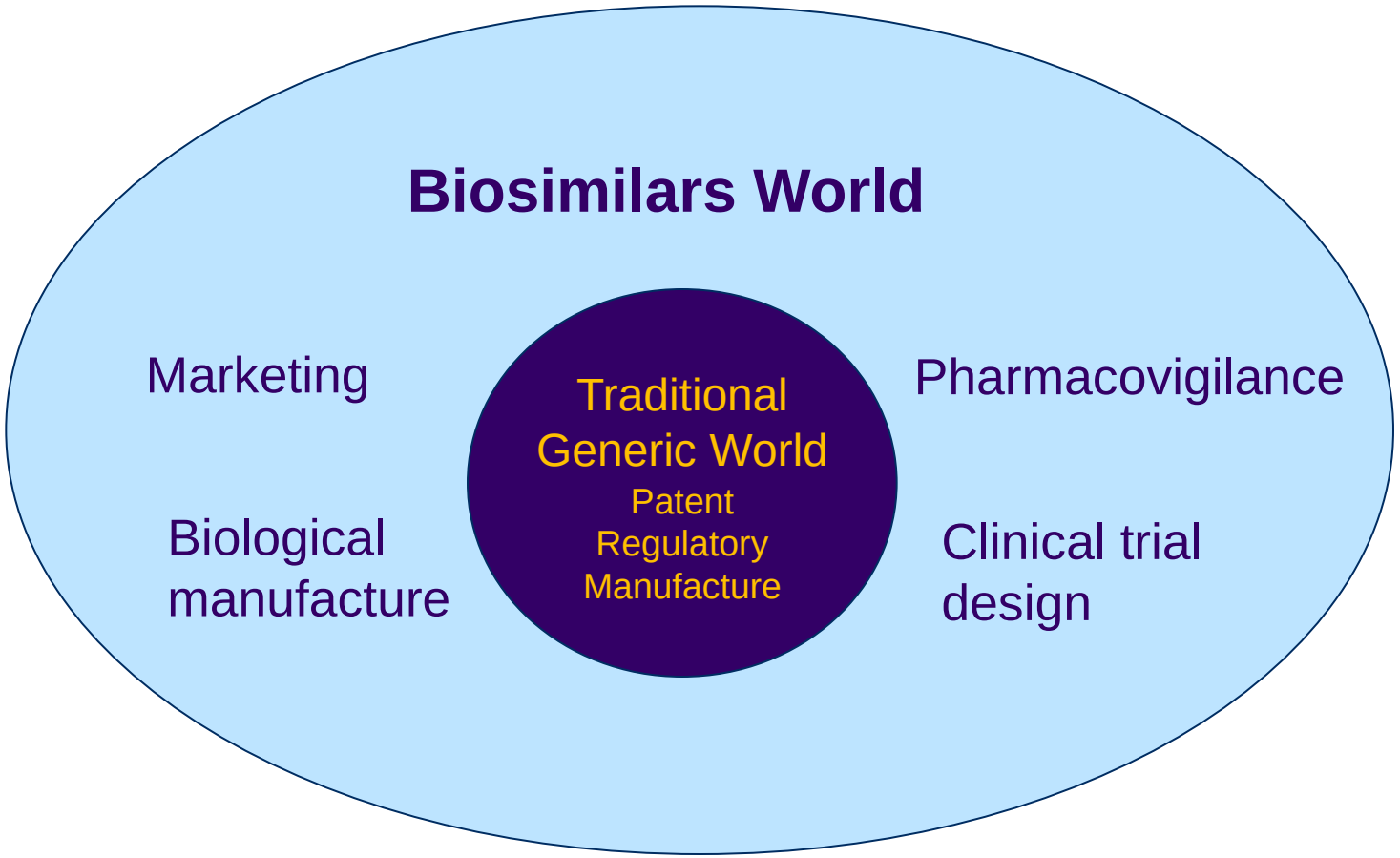
Core Competencies for Biosimilar Developers



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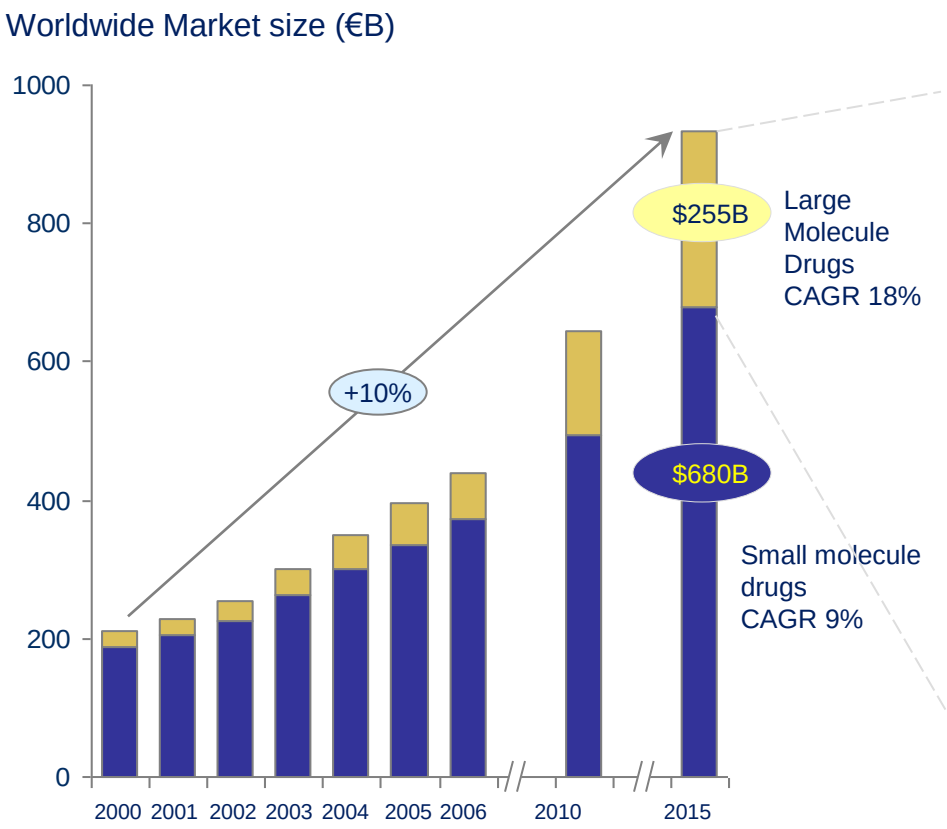
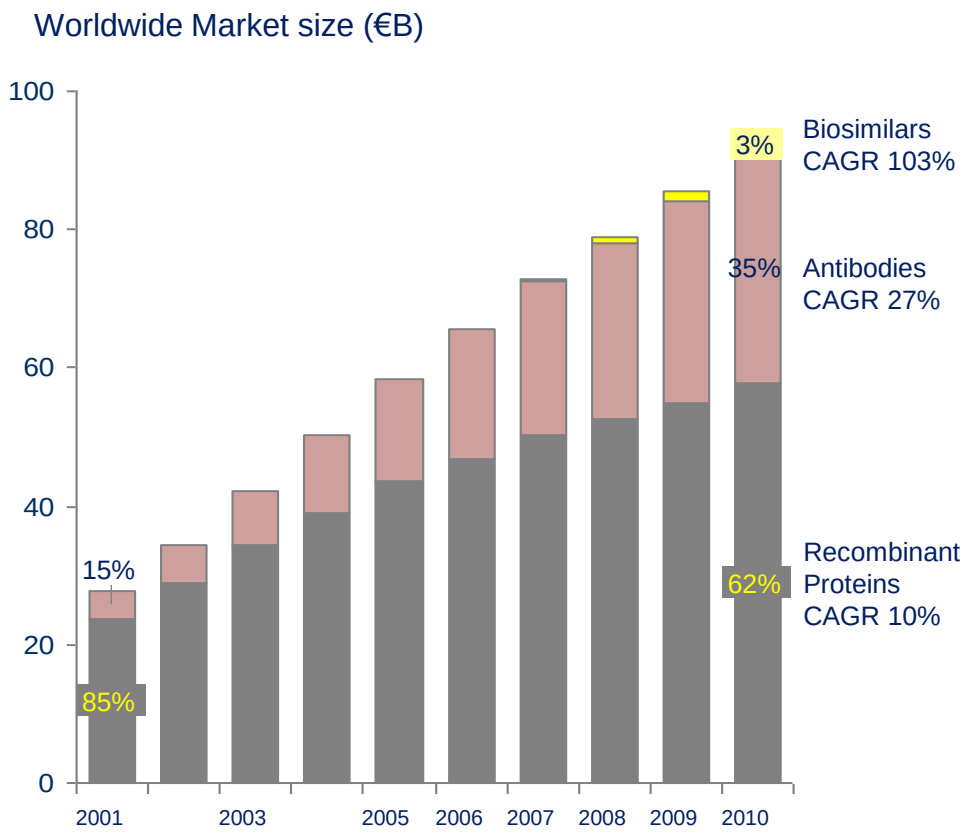
Biologics Market Growing Faster than Small Molecule Drugs

Market Size By Drug Type



Biologics Market By Segment[1]



1. 2007 to 2010 based on forecasts
Note: Biologicals from players in emerging markets, non-protein antiinfectives, vaccines, pregnancy hormones and non-protein hormones are excluded from the current analyses
Source: Datamonitor; BCG

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Biosimilars Key Drivers

- In in 2010, global pharma market reached $830 B. Biological drugs market exceeded $116 B (14%). Biosimilar drug sales $380M
- Large number of biological drug patents expire soon (>$60B by 2015)
- Increasing market demand
  - Aging population
  - Health awareness
  - Affordability and insurance coverage
- Increasing healthcare cost
- Increasing innovative drug R&D cost

⇨ affordable, safe, and efficacious biological drugs

Biosimilars would free up healthcare funds for new innovative drugs

Higher success rate, lower development cost

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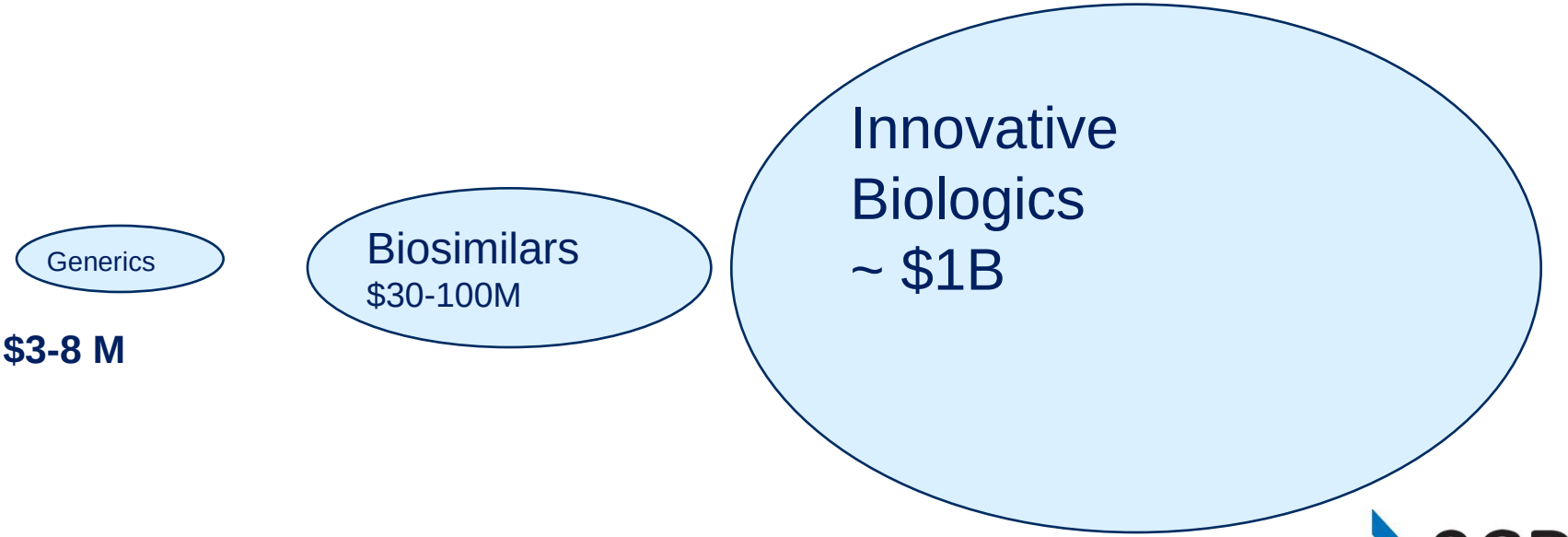
Slower and Costly



Global Status

- EU
  - EU Commission: legislative framework in 2004
  - EMEA: general guidelines in 2005
  - Over 10 products marketed since 2006 (hGH, EPO, GCSF, Insulin and IFN)
- Australia
  - Guideline established in fall 2006
  - Several biosimilar products approved
- USA
  - Congress passed the new legislation in March 2010 (12 years data exclusivity)
  - FDA working on new regulatory guidelines
- Japan
  - Guideline established in fall 2008
  - The first biosimilar drug approved
- India: active
- China: No clear guidelines available, active discussions

Criteria for Biosimilar Products

Key: comparable quality, safety, and efficacy to the reference medicine

- Non-clinical studies
  - Analytical studies: biochemical/biophysical, cellular activities and characteristics, MOA
  - Animal studies: pharmaco-toxicological assessment, clinically relevant activity
- Clinical studies
  - Comparative PK, PD
  - Efficacy (≥ one surrogate marker)
  - Safety
  - Immunogenicity
  - Route of administration, dosage form, strength
- Clinical safety and pharmacovigilance
  - Post-market monitoring
  - Risk management plan
- Manufacturing – Quality, safety, efficacy

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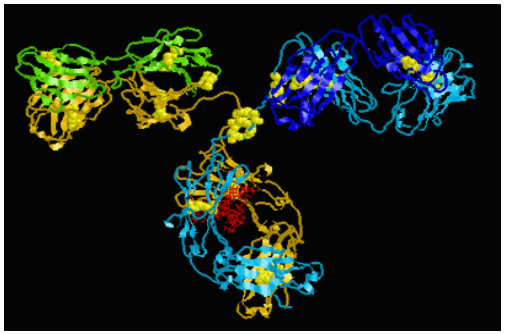
Immunogenicity – clinically relevant anti-drug antibody

- Causes of immunogenicity - complicated
  - Product related
    - structure, stability, etc.
    - Product and process-related impurity, post-translational modification
    - Route of administration, dosing regimen and schedule
  - Patient related
    - Genetic or acquired, age
    - Underlying disease and treatment
  - Ab classes, affinity, specificity
- Safety impact of immunogenicity
  - Varies from indication
  - Therapeutically irrelevant or
  - Life-threatening
    - Reduce efficacy
    - Cross-reactivity to endogenous protein
    - Serious general immune effects
  - Alters PK, PD and activity in patients



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Immunogenicity – clinically relevant anti-drug antibody

- How to reduce immunogenicity
  - In-silico modeling to identify T-cell epitopes
  - In-vitro cell-based assays to confirm/identify T-cell epitope
  - Maintain human sequence and post-translational modification
  - Reduce the impurity to the minimum level
- How to test immunogenicity
  - Develop appropriate strategy in clinical study design
  - State of art and validated screening and confirmatory assay with appropriate specificity and sensitivity
  - Sufficient patient numbers and data points
  - Justified timing of sampling
  - Consider interference from impurity and circulating antigen

Biosimilars vs Innovators

Process = product

- Production cell line
- Formulation
- Manufacture
- Route of administration

Hurdles and Don’ts

Hurdles:

- Manufacture process is complex and expensive to achieve “similar” quality, safety, and efficacy profile
- Uncertainty of regulatory pathway in US, China, and many other countries
- Non-interchangeable
- Conflicting interests among regulators, original biologics makers, insurance payers, practitioners, and patients

Don’ts:

- Don’t change primary sequence
- Don’t change major process and formulation
- Don’t change the route of delivery, dose regime and schedule
- Don’t aim at “better”, aim at “same” or “as similar as possible”

SFDA Regulatory Requirements

- Marketed product outside of China
  - Comparable manufacture process and QA/QC standards
  - Comparable biological activity in vitro and in vivo
  - 1 month tox on 1 species*
  - 1-2 efficacy models
  - Full clinical trial
- Marketed product in China
  - Comparable manufacture process and QA/QC standards
  - Comparable biological activity
  - 1 month tox on 1 species*
  - 1-2 efficacy models
  - Phase III trial

* Based on the comparability to the known drug, the pharmacology and toxicology study can be reduced or eliminated

Biological Drugs on the Market in China

- New generation of biological drugs
  - EPO, TPO, 3SBio + many developers
  - GCSF, many developers
  - Enbrel (益赛普), CITIC, Celgen
- “Legacy” biological drugs
  - Interferon
  - hGH
  - Insulin
  - Interleukins

Case Study: human erythropoietin

Biochemical Assessment of Erythropoietin Products From Asia Versus US Epoetin alfa Manufactured by Amgen

SUNGAE S. PARK,1 JIHEA PARK,1 JASON KO,2 LOUISE CHEN,1 DAVID MERIAGE,1 JILL CROUSE-ZEINEDDINI,3 WENDY WONG,4 BRUCE A. KERWIN2

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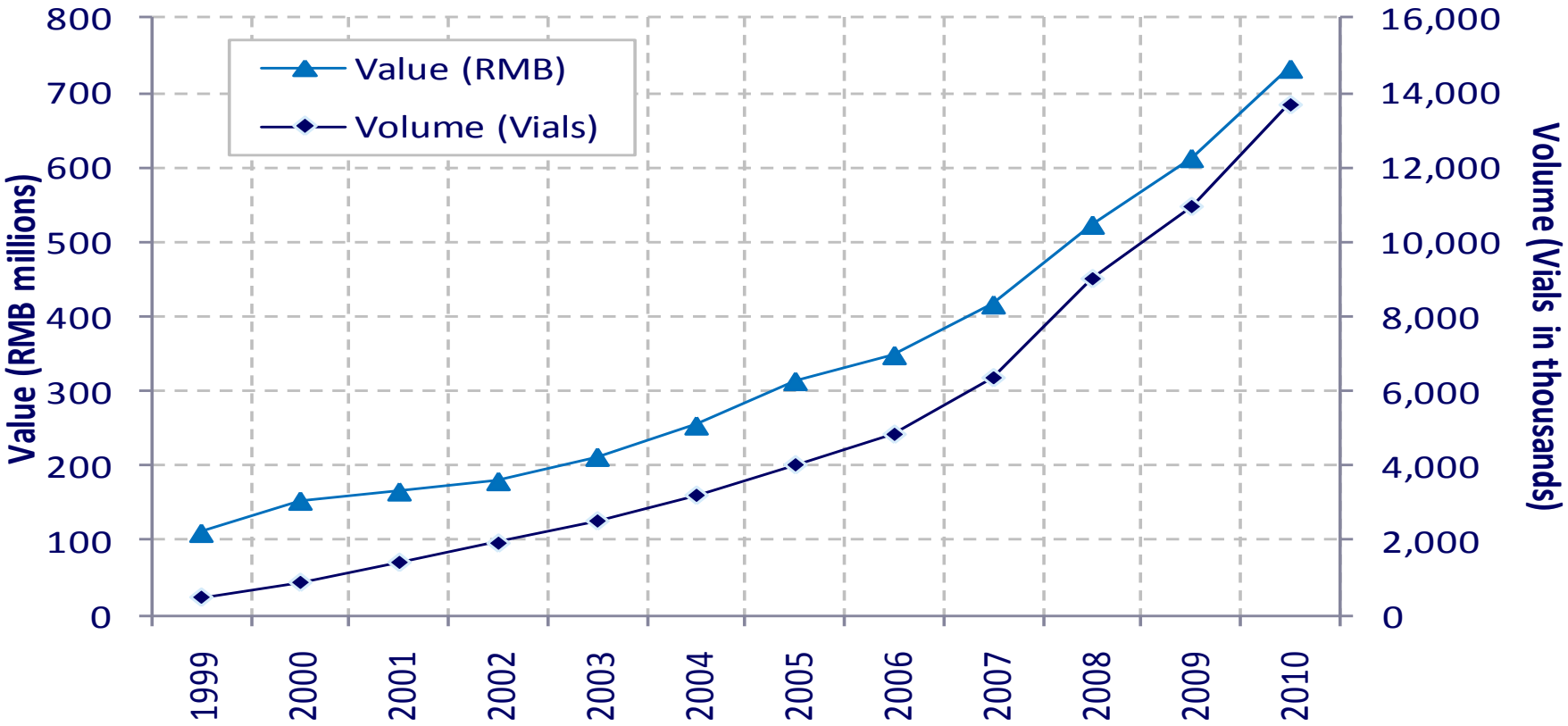
1Amgen Inc., Process and Product Development, Formulation and Analytical Resources Group, Thousand Oaks, California 91320
2Amgen Inc., Process and Product Development, Analytical and Formulation Sciences Group, Seattle, Washington 98119
3Amgen Inc., Process and Product Development, Cellular Sciences Group, Thousand Oaks, California 91320
4Amgen Inc., Department of Quality Assurance, Thousand Oaks, California 91320

Recombinant Human Erythropoietin (rHuEPO) Sample List from Asia

Marketed Country	Trade Name	Company	Exp. Date	HSA	CHO Cell	Label Conc. (IU)	Lot #	Container Type
USA	Epogen1	Amgen	August 5, 2007	Yes, 0.25%	Yes	2000	P029954	Vial
USA	Epogen1	Amgen	February 2, 2007	Yes, 0.25%	Yes	3000	P008951	Vial
USA	Epogen1	Amgen	January 8, 2007	Yes, 0.25%	Yes	10000	P028155	Vial
Korea	Eporon	Dong-A	February 2007	Yes	Yes	4000	ED50398	Vial
Korea	Eporon	Dong-A	March 2007	Yes	Yes	4000 IU/0.4 mL	PD50908	PFS
Korea	Espogen	LG	November 2007	Yes, 2.5 mg/mL	NA	2000 IU/0.5 mL	EPO05017	PFS
Korea	Epokine	CJ	March 2007	Yes	Yes	4000 IU/0.4 mL	5530	PFS
China	Epiao	SS-Pharm	November 2007	Yes, 0.25%	NA	2000	20051101	Vial
China	Jia Lin Hao	Shandong E-Hua	December 2007	Yes	Yes	3000	20051203	Vial
China	Ji Mai Xin	Hua-Bae Pharm	August 2007	Yes	NA	3000	Y20050931	PFS
China	Ji Mai Xin	Hua-Bae Pharm	September 2007	Yes	NA	3000	Y20051031	PFS
China	Huan Er Bo	Beijing Four Rings	March 2008	Yes	NA	3000 IU/0.6 mL	20060305	PFS
China	Huan Er Bo	Beijing Four Rings	February 2009	Yes	NA	3000 IU/0.6 mL	20060203	PFS
China	SEPO	China-SPG	August 2007	Yes	Yes	4000	20050905	Vial
India	Zyrop	Imported from Argentina (Bio Sidus)	March 2008	Yes, 0.25%	Mammalian	10000	H10-4031H01	Lyophilized
India	Wepox	Wockhardt	August 2008	NA	Mammalian cell	40000	XF10336	PFS
India	Shanpoietin	Shantha Biotech	April 2008	NA	Yes	4000	EPO2206	PFS
India	Shanpoietin	Shantha Biotech	July 2008	NA	Yes	4000	EPO2806	PFS
India	Epotin	Imported from China (NCPCGB)	April 2008	Yes	Yes	4000	Y20060541	PFS

EPO China Market Growth

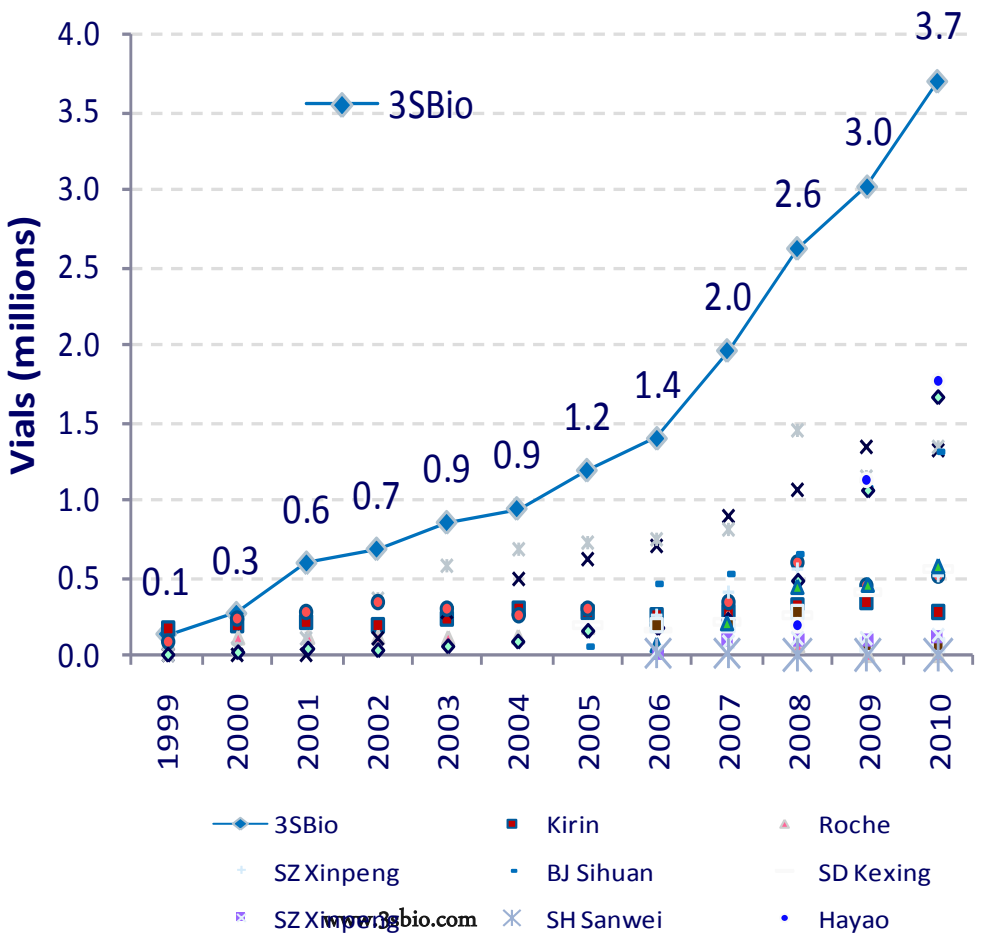
Chinese Total EPO Market in Volume and Sales (1999-2010)

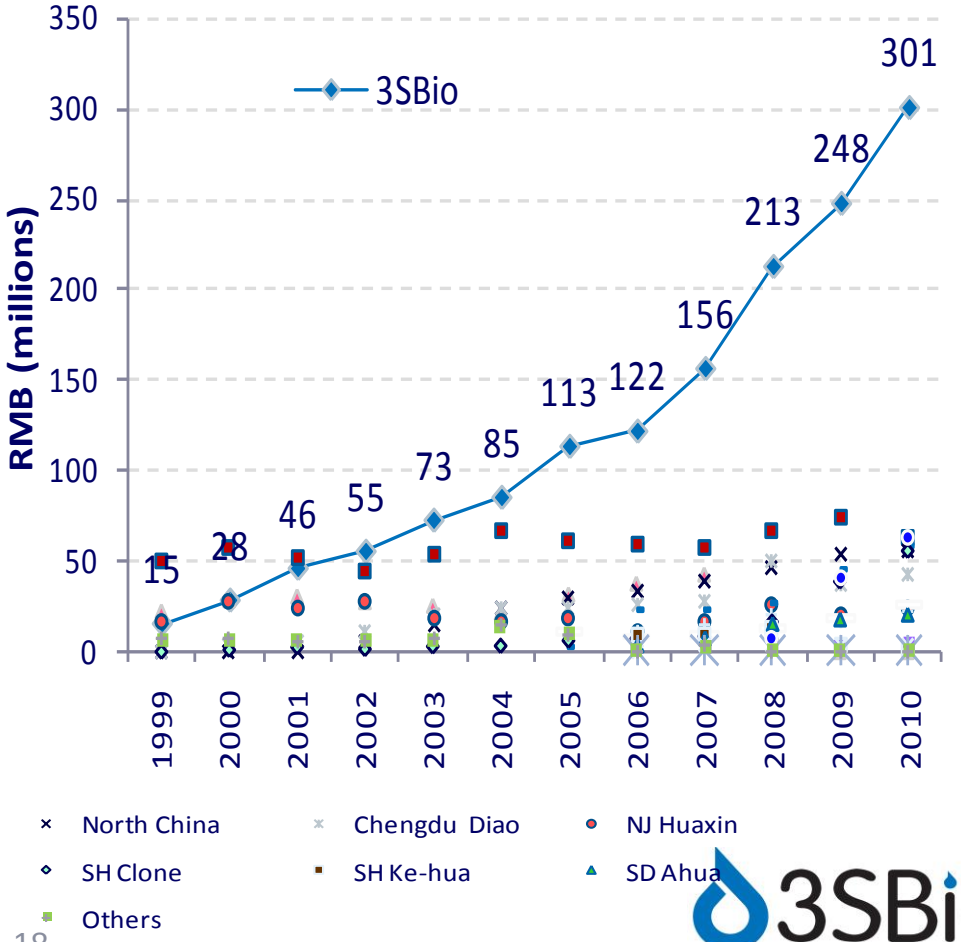


Source: IMS Health

Chinese EPO Market is Crowded

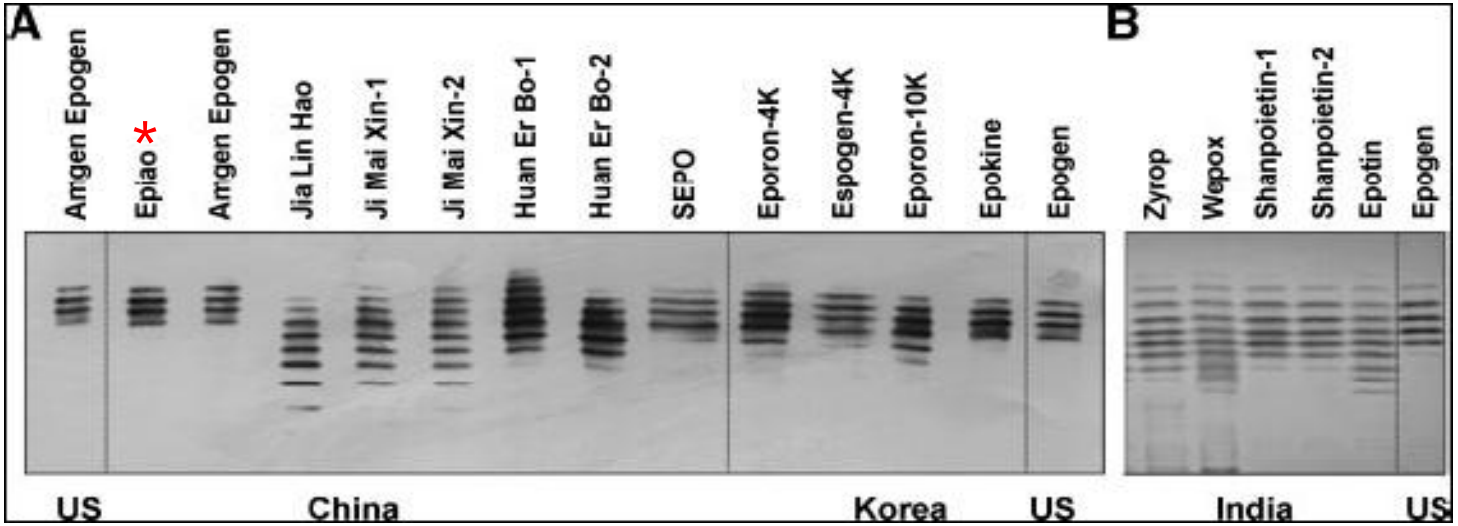
Chinese EPO Market Volume and Value (1999-2010)





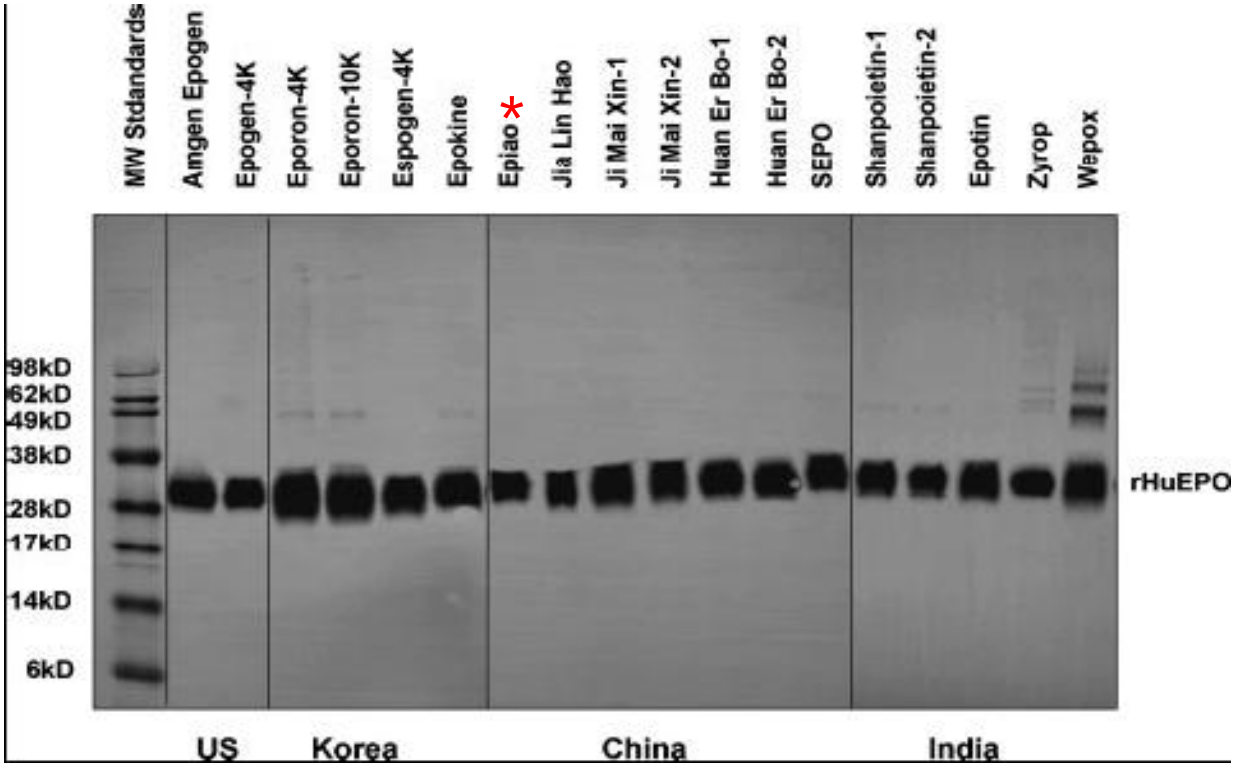
Source: IMS Health

Iso-electro-focus (IEF) Gel

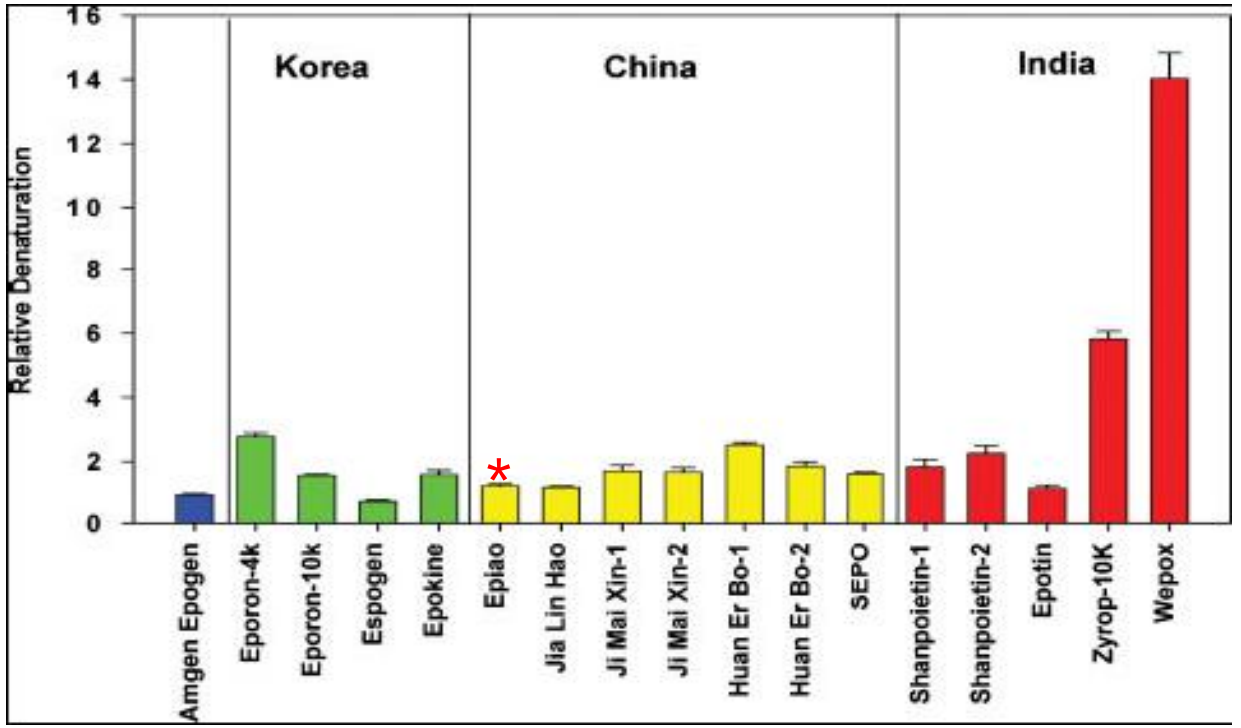


(A) samples from China (lanes 2–9) and Korea (lanes 10–13) and (B) samples from India (lanes 1–5).

SDS–PAGE with Western Blot Analysis for Aggregation



Relative Denaturation -
9G8A antibody assay to detect unfolding structure



Samples from China, Korea and India were compared to Amgen Epogen. A value of 1 indicates no difference in folding between the sample and the EPO standard

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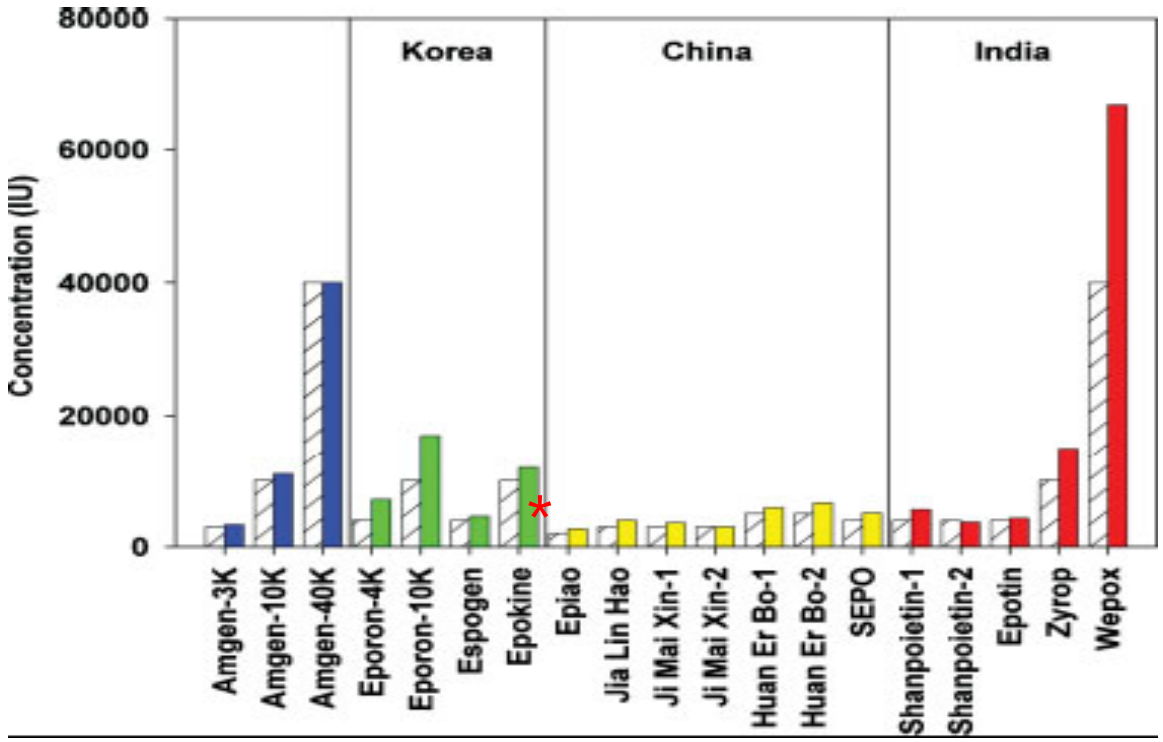
Concentration

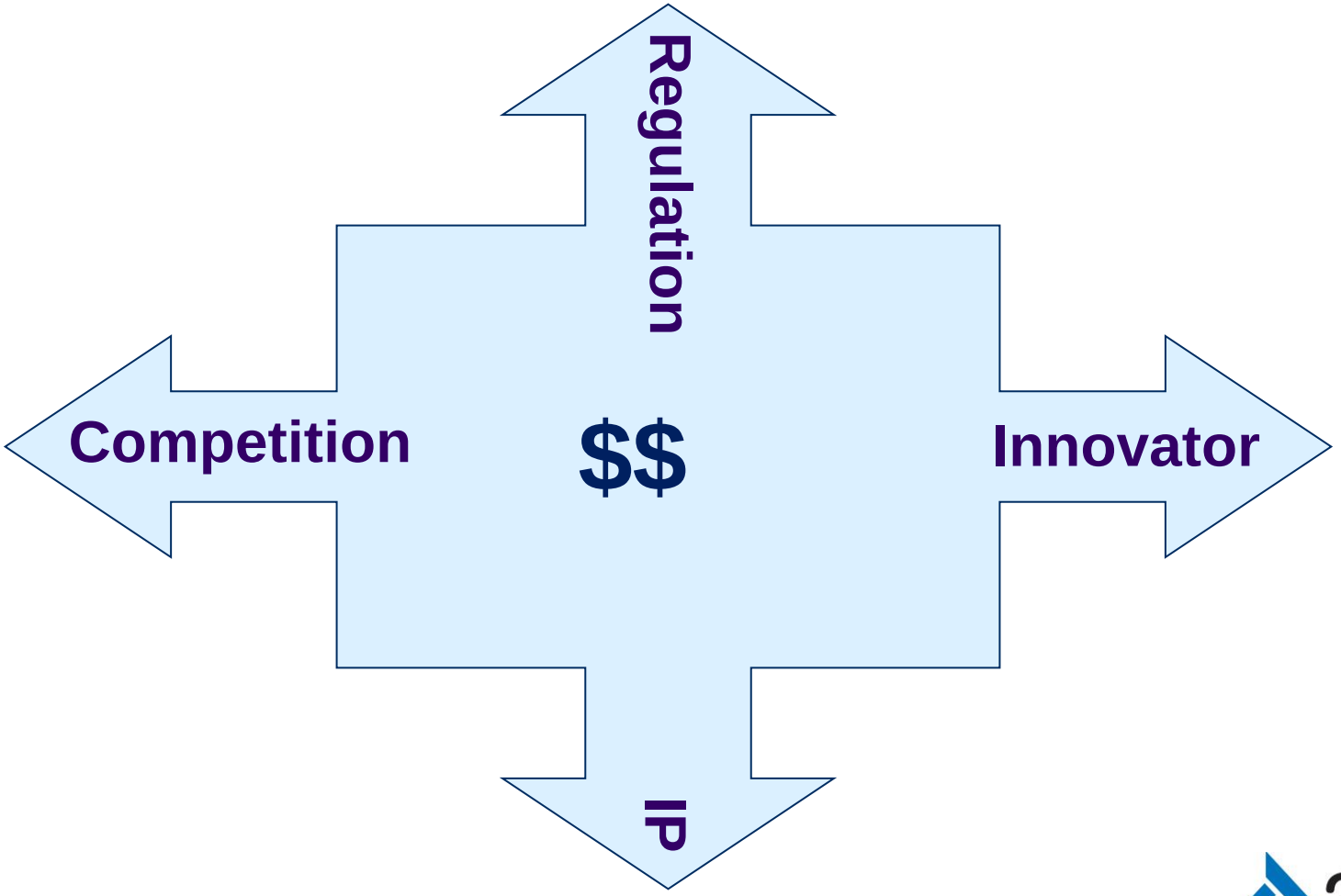


Striped bars represent the labeled concentration and solid bars represent the concentration measured by ELISA.

Conclusion

- rHuEPO from Korea, China, and India were compared with the innovator product, Epoetin alfa, in vitro for molecular integrity, glycoforms, and ELISA
- Some rHuEPO from Korea, India, and China contained more glyco-forms and other impurities
- These data emphasize potential biochemical discrepancies resulting from different cell lines, manufacturing processes, and quality control.
- These data formed the basis for a strong argument in favor of establishing high standards of quality control in product manufacturing and processing.

Challenges for Biosimilars Development



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Opportunities and Challenges

- Opportunities
  - Large market needs and growing affordability
  - Existing manufacturing technology
  - Growing understanding to biological drugs
  - Competitive pricing advantage on global market
  - Low risk low cost
- Challenges
  - Lack of clear regulatory guidance in many countries (US, China)
  - Balanced legislation which protect and promote innovative drugs
  - Complicated analytical techniques
  - Development of manufacturing capability
  - Enter the market at risk (against innovative drug and other competitors)
  - No interchangeability, brand marketing required

Thank You