Trends in research & development of biopharmaceuticals in international pharmaceutical companies

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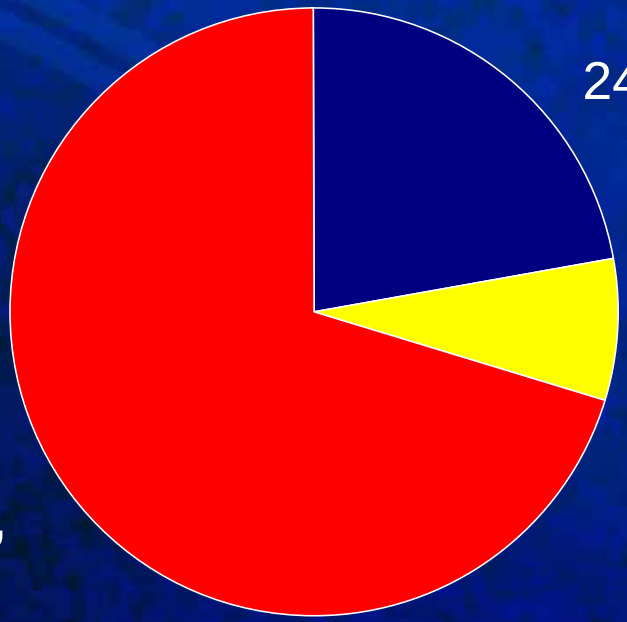
On a global basis, biotechnology projects account for a quarter (24%) of active pipelines

Worldwide R&D Pipelines June 2003



24% Biotechnology

8% Oncology Small Molecule*

Several protein drugs have achieved blockbuster drug status (>$1B/year):

EPO's, Neupogen, Anti-TNF's, Insulins, Interferons....

n ~ 5,100 Projects

Source: IMS R&D Focus June 2003. *Estimate

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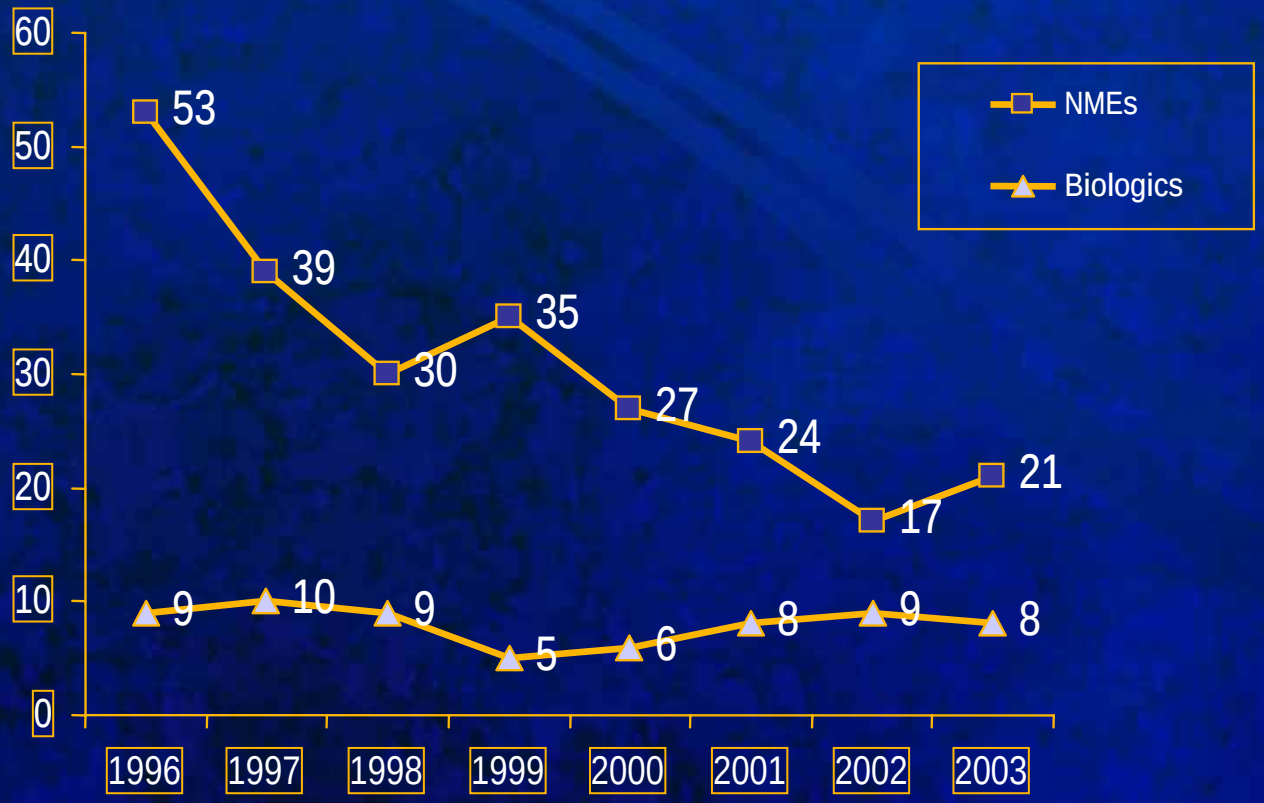
In the US, NME approval have declined dramatically, while BLA approvals have remained essentially constant since 1999



Source: FDA, 2003

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Biopharmaceutical Industry 2004 – Marketed Products

- 91 therapeutic biopharmaceutical products are approved/licensed in the US (PhRMA 2004)
  - 3 cellular therapies
  - 39 rDNA products expressed in microbes
  - 27 rDNA products expressed in cell culture
  - 22 monoclonal antibody products expressed in cell culture
- US sales expected to exceed $ 10 billion and to represent about 45% of worldwide sales for 2004

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Licensed/Approved Centocor Products

REMICADE®
INFLIXIMAB

Pr EPREX*
epoetin alfa
To Live Life

REOPRO®
abciximab

RETAVASE®
Reteplase recombinant

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Who Developed the Current Approved Biopharmaceutical Products ?

- Of 85 protein products with known development history,
  - 37 were developed by largest 7 biotech firms
  - 8 were developed by small biotech firms
  - 40 were developed by large pharma firms
    - 21 of the 40 came from 3 firms, each with 50+ years of natural protein product experience (Lilly, Novo Nordisk, Serono) who largely replaced their natural protein products with rDNA derived ones
- Large biotech firms are arguably the strongest competitors, with many large pharma firms also active

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What Therapeutic Areas Have Approved Biotechnology Products in 2004?

- 25 years ago, natural biological products were concentrated in the therapeutic areas of endocrinology, anti-infectives, and coagulation
  - It is therefore, not surprising that these therapeutic areas have the most branded products (50 of 91)
  - However, correcting for multiple brands for a few targets, only 20 therapeutic targets of 52 are in these therapeutic areas
- The march of science and medicine has also enabled biotechnology products for therapeutic targets in oncology and immunology/inflammation
  - 26 of 52 therapeutic targets are in these two new fields

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What Therapeutic Areas Have Approved Biotechnology Products in 2004?

Therapeutic Area	Brands	Products	Targets	3 or More Brands on Same Therapeutic Target
Oncology	21	21	18	Anti-CD20 Mabs (3)
Immunology/Inflammation	9	9	5	Anti-TNFalpha (3)
Endocrinology	27	19	9	hGH (8), insulin (9)
Coagulation	12	10	6	Thrombolytics (4), FVIII (4)
Anti-infective	11	11	5	IFNalpha (5), IFNbeta (3)
Other	7	7	7	

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Biopharmaceutical Industry 2004 - Products in Development

- 324 biopharmaceuticals in nonclinical or clinical development by PhRMA member companies
- Of these, 121 are novel therapeutics in the clinic
  - 11 cellular therapies (1 in late development)
  - 28 are microbially-expressed rDNA (11 late)
  - 21 are mammalian-expressed rDNA (8 late)
  - 61 are monoclonal antibodies (11 late)
- Over half the therapeutic molecules presently in the clinic are monoclonal antibodies, and two – thirds are cell culture products

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Who Are Developing Therapeutic Biopharmaceutical Products ?

- Large biotech firms are developing 35 entities (5 microbial, 7 cell culture, 23 Mab)
- Small biotech firms are developing 49 entities (15 microbial, 8 cell culture, 26 Mab) – but if promising, many are likely to be inlicensed by large biotech or large pharma for PhIII
- Large pharma are developing 18 entities (9 microbial, 4 cell culture, 5 Mab)
- US National Cancer Institute is developing 8 entities (mostly Mabs)
- 11 cellular therapies in development

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What Therapeutic Areas Have Products in Clinical Development Aimed at Novel Targets?

- Oncology – 50
- Immunology/Inflammation – 25
- Endocrinology – 2
- Coagulation – 1
- Anti- infective – 2
- Other – 14
- Clearly, oncology and immunology/inflammation are likely to see most of the new product growth in the next decade!

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Challenges for Protein Drugs

- High cost of goods and complexity of manufacturing
- Potential for immunogenicity
- Discover the right molecules as efficiently as possible

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DANGER
CONFINED SPACE
ENTER BY
PERMIT ONLY
CLEAN
2003

Future Production ?

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Cost of Monoclonal Antibody Manufacturing

- Cell Culture
  - $200 - $1000/gram
- Transgenic animals
  - ~ $50/gram
- Transgenic plants
  - ~ $20/gram

10-fold cost reduction promised

25-fold cost reduction promised

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Development challenges with Transgenics

But…

- Many regulatory uncertainties
- Non-mammalian modifications could be antigenic or affect product performance (eg, half life)
- Lack of precedent; there are no approved plant- or animal-derived transgenic products
- Cost savings may not be as large as promised

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Future Manufacturing Technologies

- Cell culture with higher cell densities reaching very high levels close to that in actual living tissue
- Bacterial expression of complex proteins such as antibodies at commercial levels
- Faster transgenic plant engineering
- Human glycosylation and other post translation modifications in non mammalian expression systems

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Challenges for Protein Drugs

- High cost of goods and complexity of manufacturing
- Potential for immunogenicity
- Discover the right molecules as efficiently as possible

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Strategies to Address Immunogenicity

- Make antibody or protein as human as possible
  - Highly successful for mAbs and soluble receptors & ligands linked to antibody Fc domains
- Formulation to minimize aggregation
- Manage dosing regimens to reduce immune response
- Identify and engineer out T cell epitopes

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Immunogenicity: Unresolved Issues

- Animal models, including non-human primates are *not* predictive of human responses to recombinant human proteins[1]
  - Differences in epitope immunodominance, MHC types, T cell receptor utilization
- Clinical cases of significant immunogenicity may be extremely rare (ie, PRCA)

[1]Bugelski and Treacy: Current Opinion in Molecular Therapeutics 2004 6 (1):10-16.

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Challenges for Protein Drugs

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Milestones in the Evolution of Protein Engineering

Therapeutics

Recombinant Protein Therapeutic: Humulin®

Therapeutic mAb: Orthoclone™

Chimeric Antibody: ReoPro®

Optimized Protein: Proleukin®

Humanized mAb: Zenapax™

Phage-evolved Antibody: Humira™

1982 1986 1989 1992 1993 1994 1997 2003

Protein /Antibody Display Libraries

Antibody Humanization

Synthetic Antibody Libraries

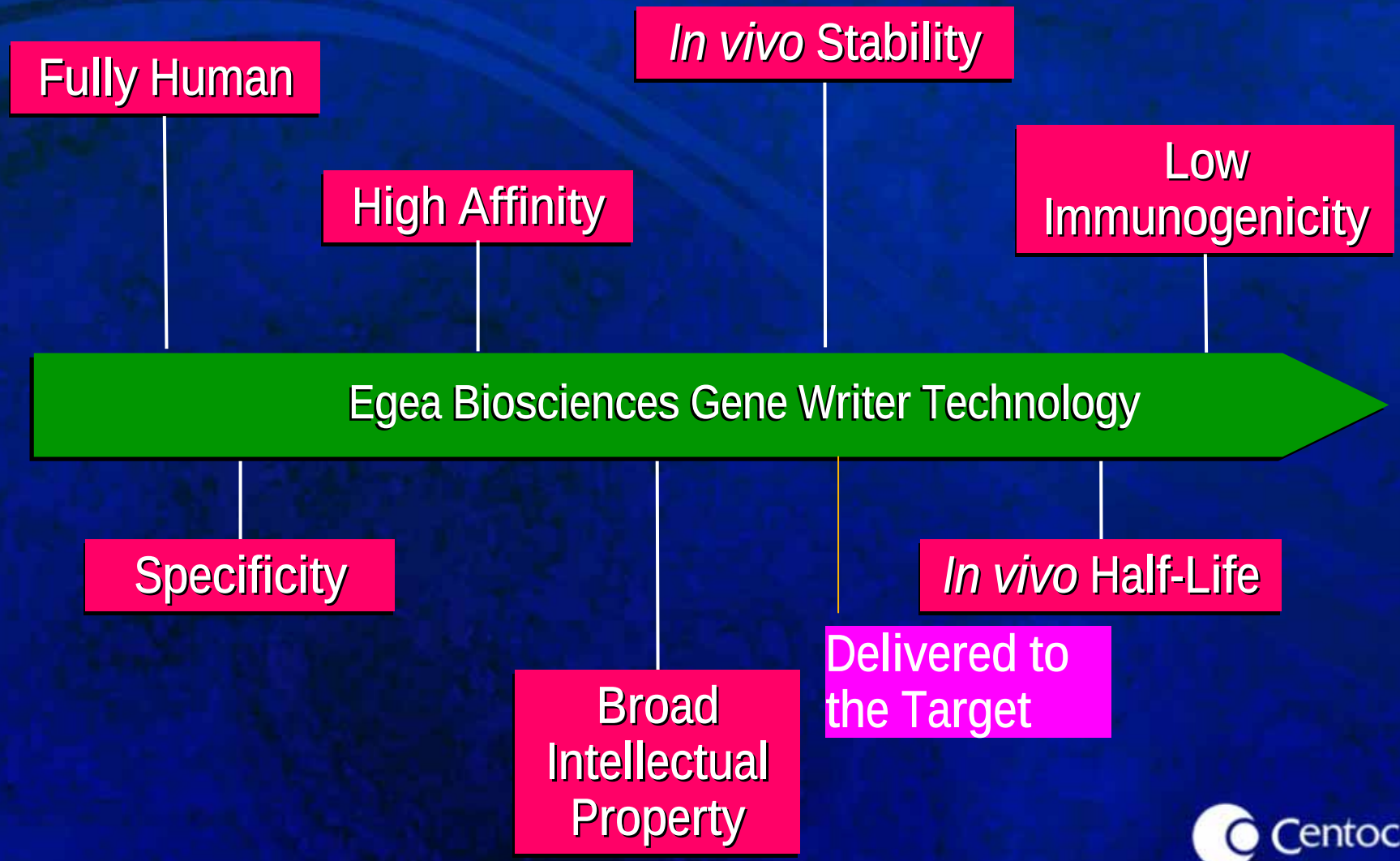
In vitro Antibody Affinity Maturation

Human Antibody Mice

Egea Biosciences GeneWriter™

Technologies

Future Centocor NME's



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Centocor Discovery Research Mission

- Create and progress innovative leads through Research into Clinical Development
- Pipeline of New Molecular Entities in development for:
  - Rheumatoid Arthritis
  - Crohn's Disease
  - Psoriasis
  - SLE
  - Pulmonary diseases
  - Cancer
  - Metabolic Diseases
  - Infectious Diseases

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A New Challenge –

Follow On Biologicals

Follow On Biologicals

- Regulators in several geographical regions are now considering the possibility of approving follow on or biosimilar biologicals along the general plan of generic chemical drugs
  - Full GMP controls & CMC package, but in some cases,
  - Less/no nonclinical data
  - Less/no clinical studies
- Undeniably, the generic drug approach generally works very well for chemical drugs; however,
- Biopharmaceuticals are much larger and more complex structures than simple chemicals

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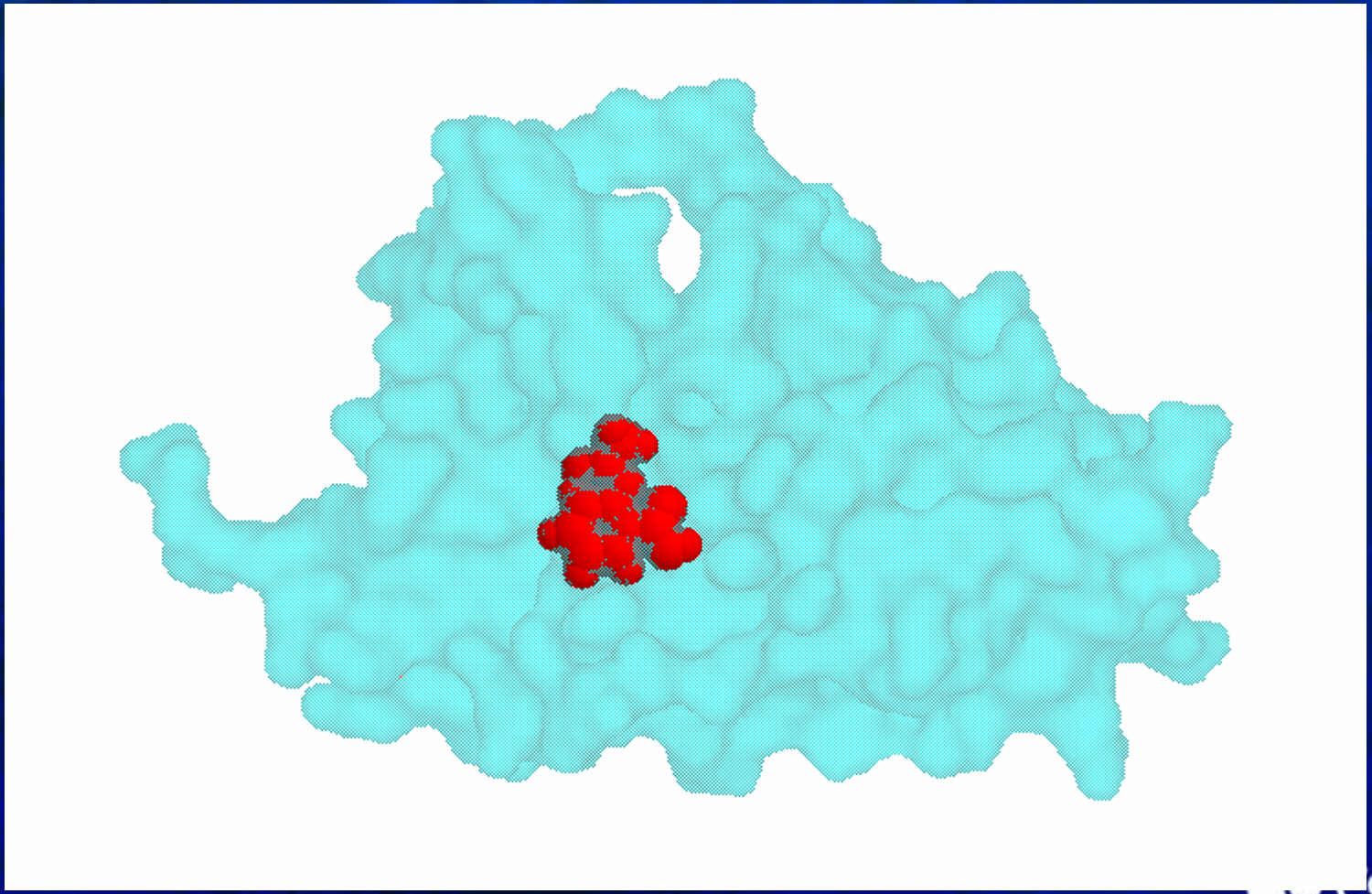
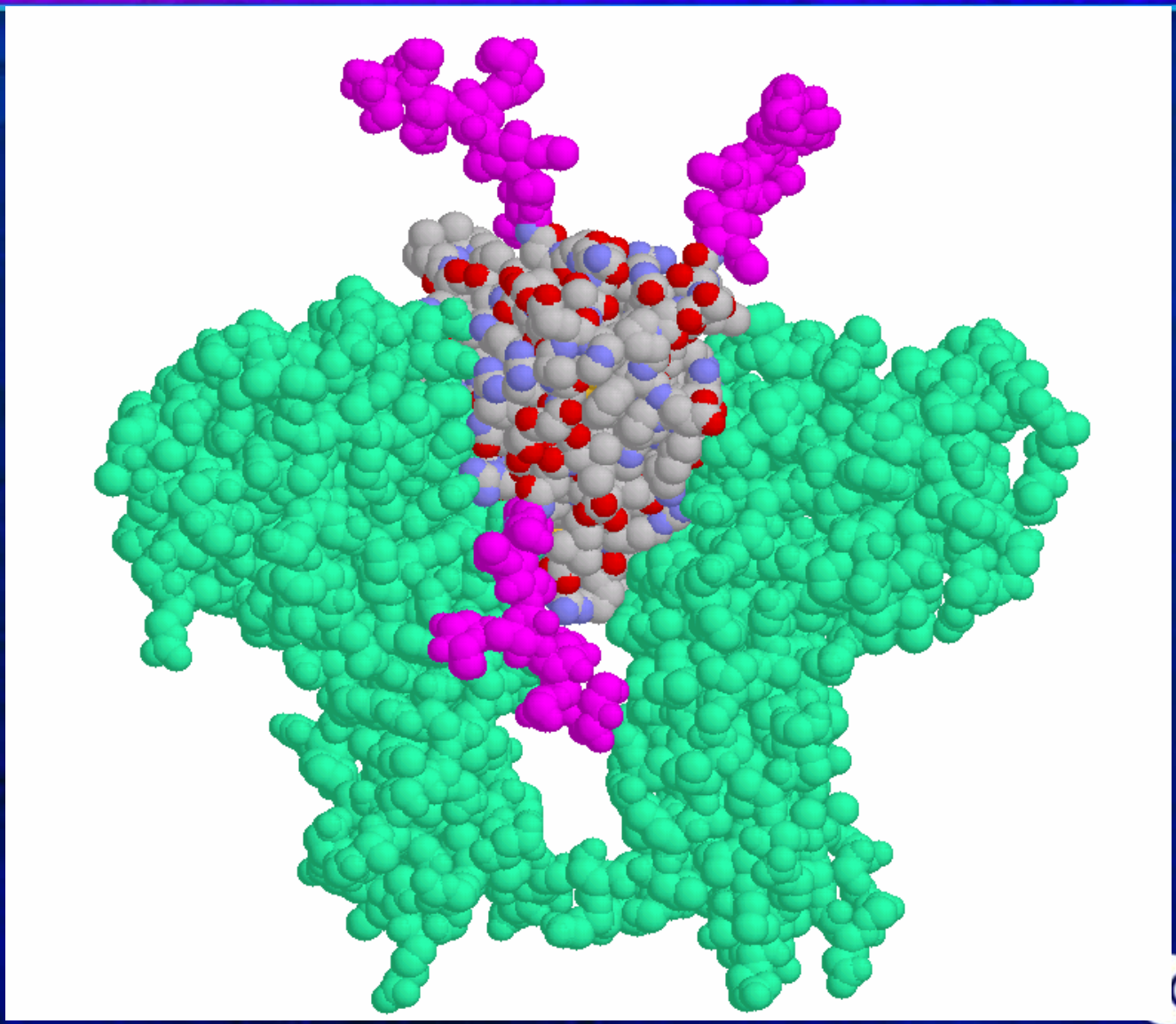
A chemical compound like Acetylsalicylic acid (Aspirin) shown in red is small and not very complex compared to EPO (Cyan)



Epoetin alpha in its receptor dimer with its three most common glycosylation sites N24, N38, N83 shown in Purple



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Follow On Biologicals

- By definition, the producer cell and the process used for the follow on biopharmaceutical product must be different from those used for the innovator product
- While it is possible to compare innovator drug product with follow on drug product, comparability studies are not possible between the innovator product and the follow on product because
  - Innovator in process materials & API & test methods are not available for comparison
  - Innovator specifications are only applicable to innovator product (and process and test methods)
- Therefore, a similar API from a different cell and a different process and a different container/closure is a different product

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Epoetin Preparations

Sample	Expiration Date	Concentration (IU/mL)	Country*
IA	April 2004	2,000	Korea
IB	April 2004	4,000	Korea
IIA	August 2003	2,000	Korea
IIB	November 2003	10,000	Korea
IIIA	January 2004	2,000	Korea
IIIB	January 2004	10,000	Korea
IV	April 2004	2,000	Argentina
V	July 2003	10,000	Argentina
VI	March 2004	4,000	India
VII	July 2004	10,000	China
VIII	August 2003	6,000	China

* Location where the marketed samples were obtained

Schellekens, H., Biosimilar Epoetins: How Similar Are They? Eur. J. of Hosp. Scien., Mar 04, 43-47.

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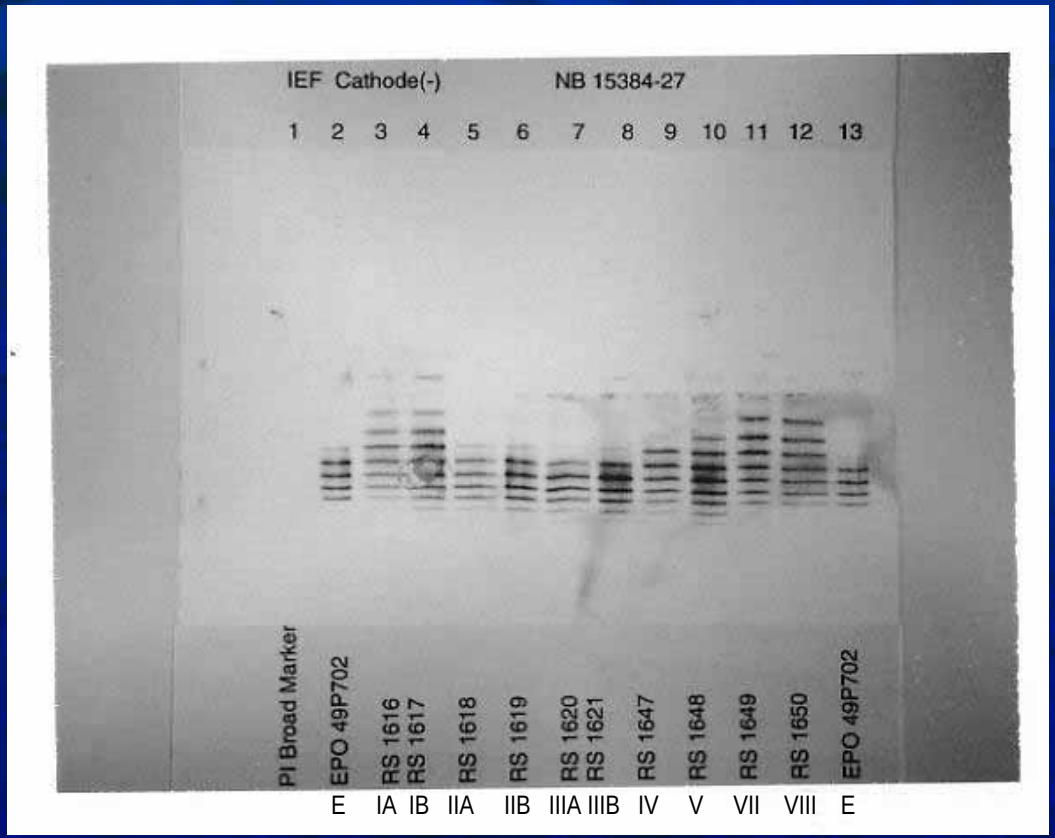
Qualitative Analysis: Isoforms

IEF / Western Blot



India Sample

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Quantitative Analysis
(Specification Ranges in Parentheses)

Epoetin Alfa Biosimilar (IU/mL)	Immunoassay (IU/mL)	In Vitro Bioassay (IU/mL)	Mouse Bioassay (activity index)
IA (2000)	2,427 **(1,800-2,400)**	3,900* **(1,600-2,500)**	1.84*
IB (4000)	6,303* **(3,600-4,800)**	7,670* **(3,200-5,000)**	1.05
IIA (2000)	2,080 **(1,800-2,400)**	1,890 **(1,600-2,500)**	1.19
IIB (10,000)	10,145 **(9,000-12,000)**	9,080 **(8,000-12,500)**	1.37*
IIIA (2000)	2,392 **(1,800-2,400)**	2,190 **(1,600-2,500)**	1.89*
IIIB (10,000)	12,457* **(9,000-12,000)**	9,900 **(8,000-12,500)**	2.26*
IV (2000)	2,045 **(1,800-2,400)**	2,130 **(1,600-2,500)**	0.99
V (10,000)	11,607 **(9,000-12,000)**	11,430 **(8,000-12,500)**	1.15
VI (4000)	5,936* **(3,600-4,800)**	11,580* **(3,200-5,000)**	0.98
VII (10,000)	10,237 **(9,000-12,000)**	13,690* **(8,000-12,500)**	0.71†
VIII (6000)	5,966 **(5,400-7,200)**	6,640 **(4,800-7,500)**	0.75†

*Markedly exceeds specification
†Fails to meet specification

Schellekens, H., Biosimilar Epoetins: How Similar Are They? Eur. J. of Hosp. Scien., Mar 04, 43-47.

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Follow On Biologicals

- The history of the past 20+ years of developing rDNA & Mab products, and making process changes, have shown that most of the time, GMP controls and data-driven comparabilty studies can manage the risks associated with process changes, but occasionally, unexpected findings occur.
- An infrequent risk for data-driven process change in an approved innovator product is different from potentially a more frequent or serious risk for a follow on product with less or no data. Patients who receive these products do not expect to assume unknown risks from products lacking the data of the innovator product.
- If follow on biologicals are to be approved without exposing patients to unnecessary risk, the safety and efficacy of each follow on product must be demonstrated in clinical studies

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