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

Worldwide R&D Pipelines June 2003

Several protein drugs have achieved blockbuster drug status (>1B/year):
- EPO’s
- Neupogen
- Anti-TNF’s
- Insulins
- Interferons...

n ~ 5,100 Projects

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

Source: FDA, 2003
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
Licensed/Approved Centocor Products

- Remicade® Infliximab
- Eprex® Epoetin alfa
- ReoPro® abciximab
- Retavase® Reteplase recombinant
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
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
### What Therapeutic Areas Have Approved Biotechnology Products in 2004?

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Brands</th>
<th>Products</th>
<th>Targets</th>
<th>3 or More Brands on Same Therapeutic Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>21</td>
<td>21</td>
<td>18</td>
<td>Anti-CD20 Mabs (3)</td>
</tr>
<tr>
<td>Immunology/Inflammation</td>
<td>9</td>
<td>9</td>
<td>5</td>
<td>Anti-TNFalpha (3)</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>27</td>
<td>19</td>
<td>9</td>
<td>hGH (8), insulin (9)</td>
</tr>
<tr>
<td>Coagulation</td>
<td>12</td>
<td>10</td>
<td>6</td>
<td>Thrombolytics (4), FVIII (4)</td>
</tr>
<tr>
<td>Anti-infective</td>
<td>11</td>
<td>11</td>
<td>5</td>
<td>IFNalpha (5), IFNbeta (3)</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
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.
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
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!
Challenges for Protein Drugs

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

- High cost of goods and complexity of manufacturing
- Potential for immunogenicity
- Discover the right molecules as efficiently as possible
Future Production?
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
Development challenges with Transgenics

But...

- Many regulatory uncertainties

- Non-mammalian modifications could be antigenic or affect product performance (e.g., half life)

- Lack of precedent; there are no approved plant- or animal-derived transgenic products

- Cost savings may not be as large as promised
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
Challenges for Protein Drugs

- High cost of goods and complexity of manufacturing
- **Potential for immunogenicity**
- Discover the right molecules as efficiently as possible
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
- 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.
Challenges for Protein Drugs

- High cost of goods and complexity of manufacturing
- Potential for immunogenicity
- Discover the right molecules as efficiently as possible
Milestones in the Evolution of Protein Engineering

Therapeutics

Recombinant Protein Therapeutic:
Humulin®

Human Antibody Mice

Humanized mAb:
Zenapax™

Phage-evolved Antibody: Humira™

Optimized Protein:
Proleukin®

Antibody Humanization

Synthetic Antibody Libraries

In vitro Antibody Affinity Maturation

Egea Biosciences GeneWriter™

Technologies

Milestones:

- 1982: Therapeutic mAb: Orthoclone™
- 1986: Chimeric Antibody: ReoPro®
- 1989: Synthetic Antibody Libraries
- 1992: In vitro Antibody Affinity Maturation
- 1993: Human Antibody Mice
- 1994: Humanized mAb: Zenapax™
- 1997: Optimized Protein: Proleukin®
- 2003: Phage-evolved Antibody: Humira™

Recombinant Protein Therapeutic:
Humulin®

Human Antibody Mice

Humanized mAb:
Zenapax™

Phage-evolved Antibody: Humira™

Optimized Protein:
Proleukin®

Antibody Humanization

Synthetic Antibody Libraries

In vitro Antibody Affinity Maturation

Egea Biosciences GeneWriter™
Future Centocor NME’s

- Fully Human
- In vivo Stability
- High Affinity
- Low Immunogenicity
- Specificity
- In vivo Half-Life
- Broad Intellectual Property
- Delivered to the Target

Egea Biosciences Gene Writer Technology
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
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
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
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.
### Epoetin Preparations

<table>
<thead>
<tr>
<th>Sample</th>
<th>Expiration Date</th>
<th>Concentration (IU/mL)</th>
<th>Country*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>April 2004</td>
<td>2,000</td>
<td>Korea</td>
</tr>
<tr>
<td>IB</td>
<td>April 2004</td>
<td>4,000</td>
<td>Korea</td>
</tr>
<tr>
<td>IIA</td>
<td>August 2003</td>
<td>2,000</td>
<td>Korea</td>
</tr>
<tr>
<td>IIB</td>
<td>November 2003</td>
<td>10,000</td>
<td>Korea</td>
</tr>
<tr>
<td>IIIA</td>
<td>January 2004</td>
<td>2,000</td>
<td>Korea</td>
</tr>
<tr>
<td>IIIIB</td>
<td>January 2004</td>
<td>10,000</td>
<td>Korea</td>
</tr>
<tr>
<td>IV</td>
<td>April 2004</td>
<td>2,000</td>
<td>Argentina</td>
</tr>
<tr>
<td>V</td>
<td>July 2003</td>
<td>10,000</td>
<td>Argentina</td>
</tr>
<tr>
<td>VI</td>
<td>March 2004</td>
<td>4,000</td>
<td>India</td>
</tr>
<tr>
<td>VII</td>
<td>July 2004</td>
<td>10,000</td>
<td>China</td>
</tr>
<tr>
<td>VIII</td>
<td>August 2003</td>
<td>6,000</td>
<td>China</td>
</tr>
</tbody>
</table>

* Location where the marketed samples were obtained

Qualitative Analysis: Isoforms

IEF / Western Blot

India Sample
## Quantitative Analysis
(Specification Ranges in Parentheses)

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

*Markedly exceeds specification
†Fails to meet specification

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 comparability 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.