

Next Generation of Biopharmaceuticals

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Summary

The annual conference of the Genomics Biotech Institute of the National Association of Managed Care Physicians (NAMCP) was held in Arlington, Va., in September 2005. This article is based on a presentation from that conference. The biotechnology industry is rapidly growing, with numerous products now marketed and under development. The expanding introduction of biopharmaceuticals will have a significant impact on all of healthcare, especially managed care.

Key Points

- Numerous additional products will be coming to market within the next decade.
- Cancer, diabetes, rheumatoid arthritis, lupus, hepatitis C, and HIV/AIDs are the targets of many of these products.
- Areas of continuing controversy related to biotechnology are follow-on biologics, stem cell research, cloning, patient access to biologics, and safety.

A LOT HAS CHANGED SINCE THE FIRST biopharmaceutical—recombinant human insulin—was approved by the FDA in 1982. Approximately 175 biotechnology products are currently marketed.¹ Around 33 products are making their way through the filing process for FDA approval. Another 426 products are in phase I, II, or III trials. All of these products are targeting more than 200 diseases including cancer, Alzheimer's, cardiovascular diseases, multiple sclerosis, HIV/AIDS, and arthritis. The rate of growth of biotechnology product approvals has skyrocketed in the last decade (see Exhibit 1).

Growth of Biotech Companies

As shown in Exhibit 2, biotechnology company revenues grew by 17 percent and personnel increased 5 percent between 2003 and 2004. Despite revenue growth, the companies continue to lose money overall. Ninety percent of biotech companies are surviving on venture capital, do not yet have a single product on the market, and are working hard to move products

through preclinical discovery and chemistry to clinical investigation and then through FDA approval.

One of biotechnology's greatest strengths is its breadth of coverage. Biotechnology companies focus on health, food and agriculture, and industrial and environmental applications. Within the healthcare-focused portion of biotechnology, many technologies are at work; see Exhibit 3. Relative to food and agriculture, companies are working on genetically modified foods and animals and a whole slate of issues that are designed to improve food supply. Industrial and environmental applications of biotechnology include renewable bio-fuels.

Products in Development

Seventy-eight vaccines for cancer are currently under development,² including dendritic, antigen-specific, and polyvalent vaccines. Antigen-specific vaccines dominate the research, representing 63 of the vaccines now in the pipeline. Of these vaccines, 18 percent are in Phase II trials; 14 cancer vaccines are in Phase III development, including five for melanoma, two for pancreatic cancer,

Exhibit 1: New Biotech Drug and Vaccine Approvals/New Indication Approvals by Year

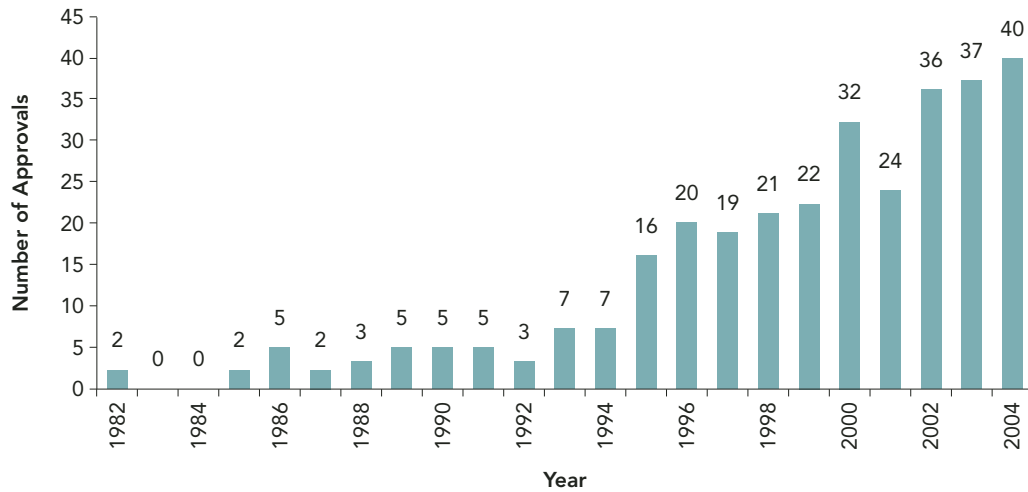


Exhibit 2: Global Overview of Biotech Companies

Public Company Data	2003	2004	Percent Change (%)
Revenues (millions)	\$46,553	\$54,613	17
R&D Expense (millions)	\$18,636	\$20,888	12
Net Loss (millions)	\$4,548	\$5,304	17
Number of Employees	174,520	183,820	5

Source: Ernst & Young

three for non-Hodgkin’s lymphoma, two for prostate cancer, and two for breast cancer. Given that approximately 50 percent of products in Phase III development eventually gain FDA approval, it is likely that seven of these vaccines will make it to market.

In addition to vaccines, there are monoclonal antibodies and antisense oligoneucleotides under development for breast cancer (see Exhibit 4). Beyond a curative treatment, the future in breast health needs to be focused on chemo-prevention, advances in diagnosis, and the potential role of complementary and alternative medicine. Several studies are evaluating alternatives to surgery and chemoprevention.

A large number of products are under development for prostate cancer (see Exhibit 4). One is a gene therapy agent. Because of serious adverse effects in some of the early trials with gene-altering agents, this type of research is proceeding quite slowly. Looking toward the end of this decade and moving into the next, there likely will be more focus on gene therapies because of expanding knowledge about the genetic

basis of disease. In the arena of prostate cancer research, an immediate goal is to determine whether widespread prostate specific antigen (PSA) screening is effective in the reduction of prostate cancer morbidity and mortality, so as to establish effective guidelines and begin implementing them worldwide. A second priority is to develop effective treatments for metastatic, hormone-refractory disease.

As with prostate and breast cancer, a tremendous number of products are under development for lung cancer (see Exhibit 4). Beyond the possibility of these products, an immediate goal for improving survival rates for lung cancer is the design and implementation of national screening programs for early detection of disease. Equally as important is the need to reduce tobacco consumption through effective educational programs. Smoking cessation, together with experimental chemo-preventive strategies, perhaps represent the most promising areas for meaningful immediate impact in this particular disease area.

In addition to the many products under development

for diabetes mellitus (see Exhibit 4), inhaled insulin was recently approved by the FDA. Exubera, an inhaled powder form of recombinant human insulin (rDNA) for the treatment of adult patients with type 1 and type 2 diabetes, is the first new insulin delivery option introduced since the discovery of insulin in the 1920s. Exubera delivers short-acting insulin via an inhaler. The safety and efficacy of Exubera have been studied in approximately 2,500 adult patients with type 1 and type 2 diabetes.³ In clinical studies, Exubera reached peak insulin concentration more quickly than regular insulin administered by an injection. Peak insulin levels were achieved at 49 minutes (range 30 to 90 minutes) with Exubera inhaled insulin, compared to 105 minutes (range 60 to 240 minutes) with regular insulin, respectively.³ In type 1 diabetes, inhaled insulin may be added to longer-acting insulins as a replacement for short-acting insulin taken with meals. In type 2 diabetes, inhaled insulin may be used alone, with oral therapy, or with longer-acting insulins. In addition to hypoglycemia, other side effects associated with Exubera therapy seen in clinical trials included cough, shortness of breath, sore throat, and dry mouth. The FDA recommends that patients have lung function tested before beginning treatment and every six to 12 months while treatment continues.

In the nearer term, the development of oral and additional inhaled forms of insulin will significantly improve the quality of life for insulin-requiring patients. New targets based on the insulin-signaling cascade are being studied, and preliminary results may have implications for the development of new therapies for diabetes. The importance of improved, patient-friendly treatment for diabetes cannot be stressed enough, given that tight control of blood glucose levels is essential for avoiding the often-devastating complications of the disease.

Autoimmune disorders, including rheumatoid arthritis and lupus, are another active area of biotechnology research. Many of the agents in various stages of development are listed in Exhibit 4. Promising future

treatments for rheumatoid arthritis include gene therapy and cytokine antagonists, as well as various combination therapies. Considerable research still needs to take place in determining the causes of autoimmune diseases. It is hoped that future developments will help prevent these devastating diseases and also be able to reverse the damage already wrought in patients.

Turning to infectious diseases, two areas of significant research are hepatitis C and HIV/AIDS (see Exhibit 4). Interferons, monoclonal antibodies, immunoglobulins, and therapeutic vaccines are all under development for hepatitis C. In addition to other products, exciting but slow work is transpiring on a vaccine for HIV.

Another topical issue is the avian influenza vaccine. Because of the potential for an avian influenza pandemic, many companies in multiple countries are working to develop an effective vaccine in as timely a manner as possible.

Controversial Issues

A great unanswered question in biotechnology involves what to do about biologic products reaching the end of patent. This year, there will be about a dozen major biopharmaceuticals coming off patent, affecting \$10 billion worth of product, including several of the most lucrative biopharmaceuticals.

Copies of biologic agents have been referred to by many names: follow-on protein products (FOPP), post-patent biologics, follow-on biologics, biogenerics, generic biologics, and biosimilars.⁵ The latter term is most common in the European Union. For this article, the term follow-on biologics will be used.

The 1984 enactment of the Drug Price Competition and Patent Term Restoration Act, popularly known as the Waxman-Hatch Act, established the process of an abbreviated new drug application (ANDA) for generic versions of all chemical drugs approved after 1962.⁶ Manufacturers need only to provide manufacturing process data to show bioequivalence to the branded drug. No comparable legislation governing biopharmaceuticals has yet been enacted. While consumer groups and purchasers clamor for cheaper biopharmaceuticals, and biotech companies fiercely guard their hard-won expertise, patents, production processes, and clinical know-how, regulation remains unsettled.⁷ Laws governing follow-ons are changing, but not as fast as the science, which is as convoluted as a folded protein.⁷

The difficulty in approving follow-on biologics is that most biologics are not well characterized. The exact structure is not known, so it is difficult to copy, unlike more traditional drug molecules that are easy to duplicate through chemistry. The major production issues with follow-on biologics is characterizing the protein and being able to duplicate the production process. The production process is 90 percent of the

Exhibit 3: Biotechnology Processes Today

- **Monoclonal antibodies**
- **Recombinant DNA**
- **Cell culture technology**
- **Cloning**
- **Protein engineering**
- **Nanobiotechnology**
 - > Systems/devices manufactured at the molecular level
- **Gene Therapy**
 - > Correction of genetic mutations contributing to disease
- **Stem cell technology**
- **Plant biotechnology**

Exhibit 4: Biotechnologies Under Development

Breast Cancer		
Type of Product	Name/Manufacturer/Clinical Trial Phase	
Monoclonal antibodies	<ul style="list-style-type: none"> • Bevacizumab (Genentech) – phase III • Adecatumumab (Micromet) – phase II 	<ul style="list-style-type: none"> • Ipilimumab (Medarex) – phase II • Pertuzumab (Genentech) – phase II
Immunotherapeutic vaccines	<ul style="list-style-type: none"> • IGN-101 (Igenon) – phase III • Theratope (Biomira) – phase III • GnRH pharmacine (Aphton) – phase II 	<ul style="list-style-type: none"> • Her-2 protein AutoVac vaccine (Pharmexa) – phase II • MVA-T54 (Oxford Biomedica) – phase II
Antisense oligoneucleotides	<ul style="list-style-type: none"> • GTI-2040 (NCI) – phase II 	<ul style="list-style-type: none"> • –ISIS-2503 (Isis) – phase II
Prostate Cancer		
Type of Product	Name/Manufacturer/Clinical Trial Phase	
Immunotherapeutic vaccines	<ul style="list-style-type: none"> • APC-8015 Provenge® (Dendreon) – phase III • CG-1940/CG-8711 (Cell Genesys) – phase III • DCVaxProstate (Northwest Biotherapeutics) – phase II • Globo H-KLH vaccine (Sloan Kettering Institute) – phase II 	<ul style="list-style-type: none"> • GnRH Pharmacine (Aphton) – phase II • L-BLP-25 (Merck KgaA) – phase II • MVA-Muc1-IL-2 (Transgene) – phase II • Onyx P (Onyx) – phase II
Monoclonal antibodies	<ul style="list-style-type: none"> • Adecatumumab (Micromet) – phase II • Bevacizumab (NCI) – phase II • Ipilimumab (BMS/Medarex) – phase II • J591 (BZL Therapeutics) – phase II 	<ul style="list-style-type: none"> • MDX-070 (Medarex) – phase II • Pertuzumab (NCI) – phase II • hLM609 (MedImmune) – phase II
Antisense oligoneucleotides	<ul style="list-style-type: none"> • GTI-2040 (Lorus Therapeutics) – phase II • GTI-2501 (Lorus Therapeutics) – phase II 	<ul style="list-style-type: none"> • OGX-011 (Isis) – phase II • Oblimersen (Genta) – phase II
Lung Cancer		
Type of Product	Name/Manufacturer/Clinical Trial Phase	
Monoclonal antibodies	<ul style="list-style-type: none"> • Mitumomab (ImClone) – phase III • Bevacizumab (Genentech) – phase II/III • 11D10 (NCI) – phase II • Cetuximab (ImClone) – phase II 	<ul style="list-style-type: none"> • Mapatumumab (Human Genome Sciences) – phase II • Nimotuzumab (Kuhnil) – phase II • Panitumumab (Abgenix) – phase II • Pertuzumab (Genentech) – phase II
Gene therapy	<ul style="list-style-type: none"> • Ad5CMV-p53 (Introgen) – phase II 	<ul style="list-style-type: none"> • INGN-241 (Introgen) – preclinical
Antisense oligoneucleotides	<ul style="list-style-type: none"> • CpG-7909 (Copley Pharmaceutical) – phase II 	<ul style="list-style-type: none"> • GTI-2040 (Lorus Therapeutics) – phase II
Immunotherapeutic vaccines	<ul style="list-style-type: none"> • IGN-101 (Igeneon) – phase III • Cancer vaccine (NovaRx) – phase II • Dexosome vaccine (Anosys) – phase II • EGF vaccine (Center of Molecular Immunology) – phase II 	<ul style="list-style-type: none"> • EP-2101 (Epimmune) – phase II • L-BLP-25 (Biomira) – phase II • MVA-Muc1-IL-2 (Transgene) – phase II • Lung cancer vaccine (GlaxoSmithKline) – phase II
Diabetes		
Type of Product	Name/Manufacturer/Clinical Trial Phase	
Insulin	<ul style="list-style-type: none"> • Inhaled (Lilly; Novo Nordisk; Aventis/Pfizer; others) – phase III 	<ul style="list-style-type: none"> • Oral (Generex; Emisphere) – phase II (US) • Intranasal (Bentley Pharmaceutical) – phase I
Growth Factors	<ul style="list-style-type: none"> • Mecasermin rinfabate (Insmed) – phase II • TH-9507 (Theratechnologies) – phase II 	<ul style="list-style-type: none"> • Protein tyrosine phosphatase 1B inhibitors • ISIS-113715 (Isis Pharmaceuticals) – phase II
Plant-derived compounds	<ul style="list-style-type: none"> • LL-2113AD (Lupin) – phase II 	
Regenerative therapies	<ul style="list-style-type: none"> • E1-INT (Transition Therapeutics) – phase II 	<ul style="list-style-type: none"> • INGAP peptide (GMP Companies/P&G) – phase II
Rheumatoid Arthritis		
Type of Product	Name/Manufacturer/Clinical Trial Phase	
Monoclonal antibodies	<ul style="list-style-type: none"> • Tocilizumab (Chugai Pharmaceutical) – phase III • Rituximab (Biogen/Genentech) – phase III • Certolizumab pegol (UCB/Nektar) – phase III 	<ul style="list-style-type: none"> • Ocrelizumab (Genentech) – phase II • HuMax-IL-15 (Amgen) – phase II • Eculizumab (Alexion) – phase II
Cytokine inhibitors	<ul style="list-style-type: none"> • AD-452 (Arakis) – phase II • AMG-162 (Amgen) – phase II • IL-1 cytokine trap (Regeneron) – phase II 	<ul style="list-style-type: none"> • K-831 (Kowa) – phase II • CDP-484 (Nektar Therapeutics/UCB) – phase II
Chemokine antagonists	<ul style="list-style-type: none"> • INCB-003284 (Incyte) – phase II 	<ul style="list-style-type: none"> • MLN-1202 (Millennium Pharmaceuticals) – phase II

Exhibit 4: Biotechnologies Under Development (continued)

Lupus		
Type of Product	Name/Manufacturer/Clinical Trial Phase	
Cytokine modulators	• IFN-alpha kinoid (Neovacs) – phase I	• Tocilizumab (Roche) – phase I
B cell targets	• Epratuzumab (Immunomedics) – phase III	• Belimumab (Human Genome Sciences) – phase II
Lupus nephritis	• Abetimus sodium (La Jolla Pharm.) – NDA filed	• Rituximab (Roche) – phase II

Hepatitis C		
Type of Product	Name/Manufacturer/Clinical Trial Phase	
Interferons	• Interferon beta-1a (Serono) – phase III • Human leukocyte interferon alpha (HemispherX) – phase II/III	• Interferon gamma-1b (InterMune) – phase II • Interferon omega (Intarcia) – phase II
Monoclonal antibodies	• XTL-002 (XTL Biopharm.) – phase II	
Immunoglobulins	• Hepatitis C immune globulin (Nabi/NIH) – phase I/II	
Therapeutic vaccines	• InnoVax C (Innogenetics) – phase II	• Transvax™ hepatitis C (Intercell) – phase II

HIV/AIDS		
Type of Product	Name/Manufacturer/Clinical Trial Phase	
Monoclonal antibodies	• 2F5 (Polymun) – phase I/II • 2G12 (Polymun) – phase I/II	• BI-201 (BioInvent) – phase I/II • Cytolin (Cytodyn) – phase I/II
Cytokines	• Aldesleukin (NIAID) – phase III • Adargileukin (Bayer) – phase I/II	• Human leukocyte interferon alpha (HemispherX) – phase II/III
Vaccines	• ALVAC HIV vaccine (sanofi-aventis) – phase III • HIV Vaccine (Oxford University) – phase II • Vacc-4x (Bionor Immuno) – phase II • Vacc-5q (Bionor Immuno) – phase II	• Tat Toxoid (Neovacs) – phase II • Ad5 HIV-1 (Merck) – phase II • IR-103 (Immune Response Corp.) – phase II

intellectual property related to the product. How this debate will be resolved is unknown. Savings related to follow-on biologics also are unknown but are unlikely to be of the same magnitude as traditional generics. In fact, because of costs related to manufacturing biologics, the savings may be quite small.

Other hot-button issues in the biotechnology industry are cloning, stem cell research, patient access to biologics, post-marketing surveillance, and safety issues.⁸ Each issue requires more public education on the value of biotechnology, including stem cells, cloning, and genetically modified plants and animals, as well as food animals that are now being cloned. The withdrawal of the multiple sclerosis drug natalizumab (Tysabri) last year because of fatal adverse effects in patients receiving the agent highlights the importance of post-marketing surveillance with biopharmaceuticals.⁹

Conclusion

Biotechnology is improving therapies through better delivery systems, better diagnostics, safer and more effective medicines, more patient access, and enhanced therapeutic options for physicians and patients. In

coming years, much potential exists for more effective, more targeted, even more individualized medical treatments that can cure or at least slow or halt disease progression. It also will be easier to determine in advance which patients will actually benefit. The 21st century is poised to be the biomedical century. **JMCM**

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