Meeting Highlights

Strategic Innovation in Health Care Delivery:
Capturing the Full Potential of Biotechnology
in Health Care

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More than 100 health care professionals convened in Philadelphia, Pennsylvania, from March 15 to March 16, 2004, to hear about the latest developments in biopharmaceuticals at a conference sponsored by the Strategic Research Institute of New York. Topics included the promise of consumer-driven health care; the trend toward increased consumer control and lower employer costs; and putting technology and evidence-based medicine into action. The speakers emphasized the rapid growth of biotechnology over the past few years and the introduction of new products to improve health care throughout the world.

Key Drivers Shaping the Health Care Industry Today

Keynote Speaker: David B. Nash, MD, MBA, Associate Dean and Chair, Department of Health Policy, Thomas Jefferson Medical College, Philadelphia, Pennsylvania.

Dr. Nash welcomed the attendees and program participants. He noted that the speakers were prepared to demonstrate that genomics research represents the solution for the diminished drug pipeline in the pharmaceutical industry. Breakthroughs in new drug development will be occurring at the intersection of human genetics, functional genomics, and proteomics.

Scheduled were sessions covering the principles and clinical utility of molecular diagnostic testing with a review of cost and current procedural terminology (CPT) coding.

“Specialty pharmacies,” which assist in dispensing biotechnology agents, enable physicians to optimize the cost and quality of care for patients receiving new and potent biological agents (“biologics”). These pharmacies are particularly suited to launches of biotechnology products and are essential in the overall success of these agents.

A panel of experts assembled to discuss the business and economics of biotechnology in terms of the importance of discovery research by smaller “biopharma” companies and the need for adequate reimbursement to justify the risks in financing new therapies. To maximize financial gain, marketing experts and proponents of drug development must agree on a biotechnology product to be introduced.

Changes in the manner in which biotechnology agents are manufactured are necessary to reduce costs. Transgenic biological agents are under investigation for making “humanized” and fully human antibodies. Many hurdles remain before these products will be acceptable for use in humans.

Part of the biotechnology equation is the regulatory body, the U.S. Food and Drug Administration (FDA), and its perception of the biotechnology industry. Granting and obtaining approvals for the new biological agents are posing serious challenges for the FDA and for pharmaceutical manufacturers.

Using Human Genetics to Improve the Safety and Efficacy of Therapeutics

Speaker: Michael Pellini, MD, MBA, President, Chief Executive Officer, Genomics Collaborative, Inc., Cambridge, Massachusetts.

As of 2004, pharmaceutical/biotechnology productivity has been decreasing because of the struggle for access to high-quality “biospecimens” and because of the problems in validating targets for biotechnology agents. The current expenditure for biotechnology drugs in the U.S. is $30 billion, with $16.4 billion directed toward research and development (R&D). Income from these drugs in fewer than 10 companies is approximately $100 billion, with a growth rate of more than 14%. There are 1.1 million employees in the biotechnology industry, and the workforce is growing at a rate of 12%.

The realities of R&D involve high risks; inflation has grown in dramatic fashion (at a rate of 12%), although R&D budgets are growing more slowly. Expectations of the new biological products by regulatory agencies and by patients may be unrealistic and might not be achievable. It appears that innovative biotechnology drugs will take longer to develop than previously anticipated.

The impact of genomics came into its own in the latter part of the 1990s; in 2001, however, only one genomic-based product was studied in humans. Only four genomic-based Investigational New Drug (IND) applications were filed in 2002, and eight were filed in 2003. Although the genomic revolution has increased the production of new potential targets because of genomic-based technologies, many false-positive and false-negative results have created a bottleneck that could slow the pace of further study.

In reality, the pharmaceutical/biotechnology industry is still considered immature, and the early expectations of rapid growth are now considered unrealistic. Research conducted in isolated “silos” has created diversified groups; that is, the tar-
gets for therapies have increased (e.g., colon and breast cancers), whereas less emphasis has been placed on the value of the targets.

In 2004, genomic research appears to be advancing with the integration of once distinct silos and with more resources directed toward genomic-based improved information technology. Genomics is no longer focused only on the early stages of R&D but, rather, throughout the entire R&D process and on the smarter and more efficient validation of targets. In addition, several positive changes in the industry have taken place:

- More than 19 genomic drugs are being tested in clinical trials.
- From 22 to 30 drugs will be entering clinical trials to treat systemic lupus erythematosus, rheumatoid arthritis, mucositis, cancers, pulmonary arterial disease, and so on.
- Drugs are becoming more specialized.
- Diagnostics are being used along with drug development.
- Drugs are being directed toward a patient’s genotype for individualized treatment plans.
- Cancers are being subtyped for better targeting of therapy.
- The use of pharmagenetic technology has helped to customize the efficacy of biotechnology products in certain patients.

Target validation is a central problem in genomic-based biological research. A glut of targets has been identified on the basis of single cell lines or tissue samples found in 0.01% of the population. There is also a heavy reliance on in vitro studies and less emphasis on work with human data that can eventually be costly and dangerous. It is imperative that large DNA sample sets from humans be analyzed in the early stages of R&D (starting in the beginning of the drug-discovery process). DNA samples must be selected, and a detailed genetics assessment of populations must be conducted; a clear correlation between genotypes and phenotypes indicates a target site for a clinical condition.

**Advances in Molecular Diagnostics and Reimbursement Challenges**

**Speaker:** Debra G. B. Leonard, MD, PhD, Associate Professor, Pathology and Laboratory Medicine; Director, Molecular Diagnosis and Genotyping Facility, Abramson Cancer Center; Director, Molecular Pathology Laboratory, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

The laboratory at the cancer center is involved in the study of DNA and RNA obtained from patient specimens to manage various diseases. Molecular diagnostics is commonly used to identify infectious diseases, including the human immunodeficiency virus (testing viral loads or genotyping).

Dr. Leonard described the coding system that is used to bill patients for tests performed. Specific CPT or International Classification of Disease (ICD) codes are used for third-party payments. CPT codes describe medical or psychiatric procedures performed by physicians and other health care providers. The Health Care Financing Administration (HCFA) developed the codes to assist in assigning reimbursement amounts to providers by Medicare carriers. Five codes are used for the eventual billing of genetic testing.

Molecular diagnostic tests can be expensive. The laboratory receives only 13% to 14% of the cost from Medicare.

Commercial diagnostic kits that use one CPT code are available. There are national limits for 14 CPT codes. For hepatitis C testing, the Medicare limit is set at $59, but the average cost is $99.18. Medicare currently reimburses hepatitis C viral load testing at about half the rate of HIV viral load testing even though similar methods are used.

Despite low reimbursements, the work continues to identify and obtain new CPT codes for new methods (e.g., microarray technologies and an expanded CPT coding system for molecular tests), and mechanisms for increasing reimbursement for existing molecular CPT codes to a level more appropriate for the cost of testing are being explored.

**The Role of the Specialty Pharmacy in Dispensing Biotechnology Drugs**

**Speaker:** Alan M. Lotvin, MD, President, Specialty Pharmacy Services, Medco Health Solutions, Franklin Lakes, New Jersey.

Specialty pharmacy is a relatively new sector for biotechnology and injectable drug products. Many different types of companies are coming together to develop systems for purchasing, managing, and administering these products. The specialty pharmacy market is currently estimated at $20 billion and is expected to reach $35 billion by 2005, with more than 22 products in 12 disease states on the horizon for that same time period.

Drugs that are handled by specialty pharmacies are generally expensive and are usually injectable; they are currently available for the treatment of chronic complex diseases such as multiple sclerosis, hepatitis C, cancer, Crohn’s disease, psoriasis, asthma, cystic fibrosis, Fabry’s disease, and rheumatoid arthritis. It has been projected that the specialty pharmacy market will exceed 16% of total U.S. drug spending by 2005. Specialty pharmacy drugs are unique: many are billable under both medical and pharmacy benefits; enhanced patient support services are required; and the average cost is $10,000 to $250,000 per year per patient.

Today, significant and costly gaps exist in the management of specialty pharmacy utilization and expenditures. Implementing a well-designed specialty pharmacy benefit management (PBM) program enables managed care organizations (MCOs) to enhance patient care while effectively managing spending across all distribution channels.

Dr. Lotvin presented a benefit management model consisting of a single-payer point of contact in which the prescription is given to one payer. Specialty drug management allows the drug benefit to be distributed across the pharmacy and medical channels. Management of the distribution channel drives prescription volume to the highest quality and is most cost-effective, eliminating drug waste because the appropriate dosage strength is used for each patient. The management model uses optimized drug selection to allow for better physician and patient communication and uses maximum allowable charge (MAO) pricing by therapeutic category. The model’s
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Design is also enhanced when benefits for plan members are optimized in terms of health and physician management. The use of specialty pharmacies helps to ensure accuracy in drug dispensing, correct bar coding, and high-quality scanning of pharmacists' badges for verification in order to provide an environment free of errors.

Examining the Business and Economics of Biotechnology

Speakers:
Matthew Rieke, MD, Principal, Quaker Bioventures, Inc., Philadelphia, Pennsylvania.
Harold Glass, PhD, Director, Pharmaceutical Business, University of the Sciences in Pennsylvania, Philadelphia, Pennsylvania.
George Tsetsekos, PhD, Dean, the Bennett S. LeBow College of Business, Drexel University, Philadelphia, Pennsylvania.

Dr. Rieke: The biotechnology industry has mushroomed since 1992; revenues increased from $8 billion in 1992 to $40 billion in 2002. There are 1,500 biotechnology companies in the U.S., and more than 340 of these are publicly held. The U.S. biotechnology industry spent $15.7 billion on R&D in 2001, and more than 155 biotechnology drugs and vaccines have been approved by the FDA. In the last six years, 70% of the biotechnology medications on the market were approved.

Venture capitalists are willing to invest in the highly risky, early-stage biotechnology companies because of the potential for profit. If potential profit is challenged, investors will move dollars out of the biotechnology industry. The environmental requirements for venture capitalists include (1) stable or increasing exit values, (2) stable or decreasing equity requirements, (3) stable or decreasing failure rates, and (4) stable or lower risk. Venture investing in medical devices was initially high, but over recent years, medical device companies have not been doing well. Reimbursement by the government for medical devices is not good, and less money is returning to venture capitalists. Development costs for FDA approval and reimbursement have also increased dramatically. The opportunity for reimbursement is critical.

Dr. Glass: Clinical investigators who use a biotechnology drug for 3, 6, and 18 months sustain a statistically significant ($P < .05$) higher product market share for the drug tested. Investigators have an impact on the success of the drug because they influence other physicians to prescribe the drug. However, investigators in contract research organization (CRO)–monitored clinical trials are less likely to prescribe the study drug after it reaches the market.

Most investigators are office-based. Peers are the most important source influencing a physician’s decision to prescribe a new drug for the first time. How often investigators prescribe a new drug is less important than what they say to other physicians, as reflected in their prescribing behavior vis-à-vis a new drug.

Company-prescribing loyalty is the single most important descriptive factor for early adopters of first-in-class new drugs. Loyalty toward a launch company is less favorable for a biotechnology company than for a regular “big pharma” company.

Dr. Tsetsekos: There is a need in the biotechnology industry to determine adequate pricing of products. Small companies enhance the marketplace, and their success is dependent on their location. Many biotechnology companies are found in the northeastern U.S. and in California, places with a high density of patients. Location can help the eventual success of a biotechnology agent.

Improving the Quality and Lowering the Cost of Future Biologics

Speaker: Richard V. McCloskey, MD, Vice President, Medical Research, Johnson & Johnson Development Corporation, New Brunswick, New Jersey.

Biotechnology products such as monoclonal antibodies and fusion proteins offer an efficacy never attained before. Toxicity is low and controllable, and patients’ lives and medical practice have been transformed. The current methods of production of biotechnology products are expensive. The solution for decreasing the costs of antibodies is to improve potency and reduce doses, use parts of antibodies, develop new low-cost production methods, or find better antibodies.

The new methods and advantages in using transgenic plant systems for maintaining efficacy and safety of biological agents are as follows:

- There are no human pathogens.
- There are no mammalian contaminants.
- Asepsis can begin later in production than is the case in current systems.
- It might be possible to achieve lower production costs and lower purification costs.

However, some uncertainties remain:

- Antibodies or proteins might be immunogenic.
- There are regulatory concerns.
- There is insufficient dialogue about transgenic plants, especially food crops, and misunderstandings abound.

Rabies vaccine and antibodies are being produced in potatoes. Vaccines have already been produced in alfalfa, tomatoes, and duckweed, and they are being studied in humans.

Health care professionals must support the research, understand the new systems, and use new products when they are approved. Industry must create platforms, and companies must make the antibodies and conduct the required biological and toxicological studies.

The Specialty Pharmacy Role in the Launch of a New Biotechnology Product: The Xolair™ Experience

Speaker: Russel Allinson, RPh, MS, Senior Vice President of Pharmacy, Priority Healthcare, Pittsburgh, Pennsylvania.

Omalizumab (Xolair™, Genentech, Novartis) is the prototypical biotechnology product that represents a new therapeutic area. This humanized monoclonal antibody is specifically designed to inhibit immunoglobulin E (IgE) and to prevent the allergic cascade of mast-cell degranulation in
patients with asthma. The product must be administered subcutaneously according to the patient’s weight and IgE concentration once every four weeks.

A specialty pharmacy is required to administer Xolair™ to ensure better control over the product in the distribution channel, to meet managed care requirements, to foster better quality and reporting of data, to achieve consistent patient care, and to encourage optimal patient adherence.

The specialty pharmacy’s role is to provide successful insurance coverage management with the use of Drug Fact Sheets, clinical management of injections through dose evaluation (using a nomogram), data capture and reporting, and patient support. The pharmacy makes sure that the drug is placed on the formulary to prevent the denial of payment, and it assists in the appeals process in case of denial of coverage or financial hardship. Specialty pharmacies have core competencies that are vital to the launching of injectable biotechnology products.

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Making the FDA Approval Process More Effective in Delivering Biotechnology Health Care
Speaker: Scott Gottlieb, MD, Senior Advisor, Medical Technology and Regulatory Affairs, Food and Drug Administration, Rockville, Maryland.

One cause of the slow approval process at the FDA is the existence of too many review cycles because of safety and efficacy concerns. The FDA is committed to reducing its review time by 10% in 2004.

For biotechnology products, pharmacogenomic data should be filed. A quality system approach by the FDA encourages new metrics to evaluate a product’s performance. An innovation proposed by the FDA is to use clinical outcomes along with surrogate outcomes (i.e., patient survival versus shrinkage of tumors). Biomarkers can be used as clinical outcomes and better measures of toxicity. Measuring biological agents for impurities slows down drug approval, and better science is needed.

Imaging technology has been proposed to achieve improved clinical outcomes for such illnesses as Alzheimer’s disease, depression, schizophrenia, and dementia. Molecular technology would be used to measure the penetration of a given product into tissues (for example, bone), to determine tumor shrinkage with x-rays, and to evaluate glioblastomas with functional magnetic resonance imaging (fMRI).

Although generic biological agents are not available, they would probably be only slightly less expensive than the brand-name products.

Keynote Address: Translating Genomic Knowledge into Health Benefits: Beyond the Human Genome
Speaker: Eric Green, MD, PhD, Scientific Director, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland.

The human genome was sequenced in 2003. The current major areas of genomic research are the need to identify (1) all functional elements in the human genome and (2) the genes that make proteins from one generation to the next. A large part of biological complexity is not in the genes; rather, it has to do with regulatory elements and noncoding functional elements. As a result, it is important to find these sequences and to be able to recognize them when new ones are found.

Gene-prediction software is marvelously advanced for finding genes but woefully inadequate for finding noncoding functional elements. The problem is that there are no good gold standards. There is not a single region in the genome where all the functional elements are known. Many people thought that by sequencing the mouse genome, all the important regions would be found. Clearly, that is not true.

Computer-aided sequence analysis may be used to compare human and mouse genomes. It is known that approximately 40% of human and mouse [genomes] are aligned and that 5% of that similar sequence is functionally important (e.g., for encoding proteins). But how does one extract that 5%? There must be some way to discriminate between regions that are similar (but not necessarily significant) and those that are important.

Part of the problem in studying the genome is that it is very large and full of “noise” (or what used to be called “junk” DNA). It is sometimes extremely difficult, at this point, to distinguish what is important from what is not. There is also a need to generate a genome parts list.

Virtually all diseases (e.g., cystic fibrosis, diabetes, arthritis, cardiovascular disease, asthma) have a genetic component. By translating genomic knowledge to medicine, we might be able to improve human health. In addition, diagnostics in the genomic era are exciting because they can improve our understanding of genetic defects. Ideally, pharmacogenomics will lead to matching an individual’s drug therapy to his or her genes.

Biotechnology Health Care: A Market Poised for Explosive Growth
Keynote Address Speaker: Francoise Simon, PhD, Professor of Business, Columbia University, New York, New York.

The focus of R&D in the post-genomics era is shifting from populations to individuals. This change presents a challenge to the traditional blockbuster brand drugs, which must make way for the targeted brand therapeutic agents, marketed globally to genotype-specific segments. Despite the increasing importance of the targeted model, an absolute shift to this model is unlikely. However, big business factors will continue to drive mass-market blockbuster drugs. One factor is that the patents on several drugs, worth $100 billion in this decade, are scheduled to expire, and companies will thus feel the pressure to develop new blockbusters.

It must be realized that post-genomic technologies have a long-term payoff and are expected to raise R&D costs and risks in the short term (i.e., in the next three to five years) as the number of drug targets rises from the current 500 to more than 5,000. Mergers of large drug companies have increased the scale and the need for growth. Marketing costs have risen since the late 1990s and have, in the U.S., been driven by such factors as the use of direct-to-consumer advertising that have not been successful.
Targeted drugs have a higher return on marketing investment than mass-market products because the focused model is much more cost-effective. The physician audience for a targeted brand might be as small as 5,000 specialists worldwide who are reachable with a small, highly trained sales force; in contrast, a 3,000-person sales force is necessary to promote primary care brands in the U.S.

Patient pools for biotechnology drugs tend to be small and highly motivated, and these patients are more effectively reached via the Internet than by expensive mass media. Targeted therapies are often supplied directly to physicians or hospitals, and the wholesaler share of profits is thereby eliminated. Because customized drugs are largely breakthrough products, they can command high prices.

Bioscience is driving innovation across industry sectors, and the result is the emergence of "biobrands," which range from bioengineered tissue to molecular diagnostics and drug–device combinations. These new biobrands will increasingly rely on evidence-based medicine, although experience-based marketing will continue to play a role. Products that address critical therapeutic areas, such as oncology, will require evidence-based marketing, whereas products that address primary care diseases, such as allergies, may benefit from a combination of evidence-based and experience-based marketing.

The growth of biotechnology products is explosive. Boundaries are fading between the biotechnology and pharmaceutical sectors as top-tier biotechnology companies have turned into full-fledged biopharmaceutical companies: Amgen’s market capitalization now tops those of Roche and AstraZeneca. In 2002, eight biological agents were in the billion-dollar club, and many have a pattern of sustained high growth, given that they target critical therapeutic areas and have limited competition. Advances in genomics have opened the door for the development of medications designed to target specific genotypes, resulting in more rational drug designs.

**Delivering the Future of Health Care**

Speaker: Gary Reedy, PhD, Vice President, World Wide Bio-pharmaceutical Public Policy, Ortho Biotech Products, Bridgewater, New Jersey.

Biotechnology companies must work with government agencies and with patients to obtain approval of their biological agents. The pharmaceutical industry is experiencing a transformation because of the growth of innovative biotechnology products. These products are moving from research to manufacturing in rapid order.

The time from initial development to approval is lengthening because of the complexity of these large-molecule biological agents, compared with the smaller synthetic molecules; however, there are post-marketing requirements for additional safety and efficacy studies of the new products.

These innovative products provide important benefits for patients with cancer, pain, arthritis, and asthma. They have increased the life expectancy in the U.S. by 1%, which has added $400 billion to the U.S. economy.

In 2004, there will be a greater number of newer large-molecule biotechnology products than the smaller-molecule agents that have dominated the pharmaceutical industry for decades. It is expected that 30% of biotechnology products will be approved when biopharmaceutical companies team up with the large pharmaceutical companies. These collaborations are growing stronger and are expected to provide the base for future therapeutics in the U.S. Companies with dual drug and diagnostics units and devices will probably have a significant advantage in the pharmaceutical industry. The large pharmaceutical companies are looking to biotechnology companies to fill their pipelines of potential drugs. Johnson & Johnson is an example of a large pharmaceutical company with biotechnology alliances.

**Patent Medicines: Why Do They Cost So Much?**

Speaker: Kate Murashige, PhD, JD, Partner, Morrison & Forester, San Diego, California.

Patent medicines are expensive for consumers. After FDA approval, there is a 20-year patent life for new chemical or biological compounds. The 20-year monopoly is considered a **quid pro quo** for full disclosure of the invention to the public. The pharmaceutical companies have responded to criticism of their high drug prices by revealing the cost—$500 to $800 million—required to bring a drug to market (including failures). Sales of a successful drug, such as omeprazole (Prilosec®, AstraZeneca) or fluoxetine (Prozac®, Eli Lilly) are computed in the billions of dollars a year. Those billions would not be forthcoming were it not possible for the patent holder to exclude competition.

The rationale behind protection for genomics-based inventions should be contrasted with what has been used to justify “strong” patents on pharmaceuticals in the traditional sense. Bevacizumab (Avastin™, Genentech), a recently approved anti-angiogenesis drug used for treating colon cancer, costs $80,000 per year to use. Epoetin alfa (EPO) is a genetically engineered version of a natural hormone, erythropoietin, which stimulates the bone marrow to produce red blood cells. In 2004, Epogen® (Amgen) and Procrit® (Ortho Biotech) showed combined sales of $8.1 billion.

Under U.S. law, patent holders are not obligated to permit others to practice the patented technology during the patent term or to grant any license to others; indeed, they are not required to practice this technology either. Although it is difficult to document the case of a valuable research tool that has been simply allowed to lie fallow, this is at least a theoretical possibility. It might be that only the pressure exerted by institutions such as universities and the National Institutes of Health has resulted in at least the potential availability of licenses on almost every research tool that is not being directly exploited for commercial purposes by its developer.

When patents expire, generic drugs can be introduced for marketing by the simple filing of an Abbreviated New Drug Application (ANDA). To earn the FDA’s approval, the generic drug must simply show bioequivalence to the pioneer drug. Generic drugs are winning the battle for ANDAs in the courts. They are prevailing 75% of the time; patent holders are not prevailing. Patents are expensive (e.g., $500,000 for both U.S. and international rights), adding to the cost of patented medications.
Health care in the U.S. is becoming unaffordable. The new realities shaping the early 21st century are epidemics of chronic diseases and an aging population, post-genomic prevention strategies transforming medicine, information technology expanding potential reach, a well-informed public that has become eager participants in its own health care, feasible evidence-based outcomes, and the trend of payers demanding safety and value in their health care.

Approximately 125 million Americans have chronic diseases, and more than 50% have multiple conditions. Ninety-five percent of spending is devoted to treatment, with little going toward reducing unhealthy behaviors (e.g., poor diet and lack of exercise). Patients with five or more chronic conditions visit 13 different doctors a year. In 2010, the baby-boomers will turn 65 years of age. America cannot afford all the diseases that it is generating.

With the use of biotechnology methods, young men and women would be prospectively examined for early detection and early intervention in the case of a chronic condition. Disease might be delayed with individually tailored medications. Thus, the focus of treatment would be shifted from intervention to prospective medicine.

“Biomonitoring” of patients would be possible by means of sensors and information technologies centered in the home for individual therapy that would be tailored to the unique characteristics of the patient’s disease. Electronic medical records would be available to all patients, and they would choose who had access to their records. Evidence-based medicine is the integration of clinical expertise, patient values, and best data into the decision-making process for the care of each patient.

The focus of health care in the future will shift from treating single diseases to customizing treatment to meet the needs of individual patients. Consumer-managed care will empower enrollees by shifting control to patients. This shift can be accomplished by supplying information on health and therapy, providing decision-making tools available on the Internet, offering incentives for patients to improve their health, motivating patients to make better choices and to spend money wisely, and rewarding quality and excellence.

Consumers are more savvy and demanding, and they are ready to take responsibility for their health.

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