Characteristics of and Trends in the Late-stage Biopharmaceutical Pipeline

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Objective: To quantify and characterize biopharmaceutical agents and new indications in late-stage development in the United States as of May 2006.

Study Design: Review of drug development databases and other secondary sources.

Methods: *Biopharmaceutical* was defined as "any biology-based therapeutic that structurally mimics compounds found within the body." Unique biopharmaceuticals, including new molecular entities or new indications in phase 2 or higher development, were identified and characterized through reviews of the literature, 5 drug development databases, a clinical trial database, and telephone inquiries with manufacturers.

Results: As of May 2006, there were 111 unique biopharmaceuticals in late-stage development for 190 indications. Of 111 unique agents in the pipeline, 87 are new molecular entities, and 24 are already approved for other indications. Overall, 38 disease categories were targeted, and at least 33 physician specialties are likely to be affected. The greatest proportion of agents (43 biopharmaceuticals and 83 indications) target cancer. More than 70% of agents in the pipeline will require administration by a healthcare provider. More than 50% of the indications in the pipeline will require long-term (chronic) treatment (defined as >1 year and excludes cancer).

Conclusions: The steady growth of the US biopharmaceutical pipeline and consequent anticipated near-term approvals will increasingly affect third-party portfolio decision making. Cost of therapy, identifying the right drug for the right patient, and outcomes-based value should drive that decision process.

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The growth of the biopharmaceutical pipeline and consequent approvals has increased each year from the first approval of human insulin in 1982. The growth of biopharmaceutical approvals is predicted to grow at a rate of 16% to 30%, compared with about a 4% growth of traditional small-molecule biopharmaceuticals.[1-3] In 2003, a study[4] was undertaken to quantify and characterize the biopharmaceutical pipeline as a means to prepare third-party payers for the unique challenges posed by availability of these agents, including appropriate use, per-patient and aggregate costs, utilization management, site of care issues, product delivery, and incorporation of these agents into existing benefit and information technology structures. The present study was undertaken to answer several questions. Like the development of traditional small-molecule pharmaceuticals, do we see a similar leveling off in the biopharmaceutical pipeline? If not, are there characteristics beyond those identified in 2003 that require the attention of third-party payers? Finally, is there a profile or a growing trend within the biopharmaceutical pipeline that we can identify early to proactively prepare for the landscape of the near-term future biopharmaceutical market?

In this study, *biopharmaceutical* is defined as "any biology-based therapeutic that structurally mimics compounds found within the body."[4(pS124)] This includes recombinant proteins, monoclonal and polyclonal antibodies, peptides, antisense oligonucleotides, therapeutic genes, and certain therapeutic vaccines. The basis for the definition is previously described.[4]

Agents were defined as *late-stage* biopharmaceuticals if they had been tested in a completed phase 2 clinical trial, were in a phase 2/3 or 3 clinical trial, or had been submitted for regulatory approval by the US Food and Drug Administration (FDA) for an unapproved indication as of May 2006. The data variables for this study include generic and brand names, manufacturer, stage of development, class of agent, target indication and disease, probable method of administration (eg, subcutaneous, intravenous, etc), physician specialty likely to use the agent for the indication, expected setting of administration (eg, ambulatory care, hospital inpatient, etc), proposed frequency of administration (eg, acute, chronic, etc), and whether the agent was already FDA approved for 1 or more other indications. Because of the frequent incongruence of information in different sources used to collect these data, numerous sources were consulted.

In this issue
Take-away Points / p229
www.ajmc.com
Full text and PDF

METHODS

Five drug development databases and other secondary sources were reviewed. The 5 databases included *eKnowledgebase* (Canon Communications Pharmaceutical Media Group, Newtown, Pennsylvania), New Medicines in Development (PhRMA, Washington, DC), R&D Focus (IMS Health, London, England), Adis R&D Insight (Wolters Kluwer Health, Yardley, Pennsylvania), and Investigational Drugs (Thomson Scientific, Philadelphia, Pennsylvania). Other sources included clinical trials data (http://clinicaltrials.gov/ and http://www.centerwatch.com/), manufacturer Web sites, press releases, analyst reports, and regulatory filings. Telephone inquiries with manufacturers were used to verify select data.

RESULTS

As of May 2006, there were 111 unique biopharmaceuticals in late-stage development in the United States targeting 190 late-stage indications in 38 disease categories. Of 111 unique agents, 87 are new molecular entities, 24 are already approved by the FDA for other indications, and 25 have completed Phase 3 trials.

Cancer (including primary therapy and supportive care applications) is the most common disease category target for biopharmaceuticals (Table). Immune-mediated inflammatory disorders constitute the second largest disease target (by category); more than 20% of agents in the pipeline target a range of these inflammatory diseases. Examples include rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, type 1 diabetes mellitus, and multiple sclerosis. Like cancer, immune-mediated inflammatory disease represents a significant clinical and economic burden to the US healthcare system.[5]

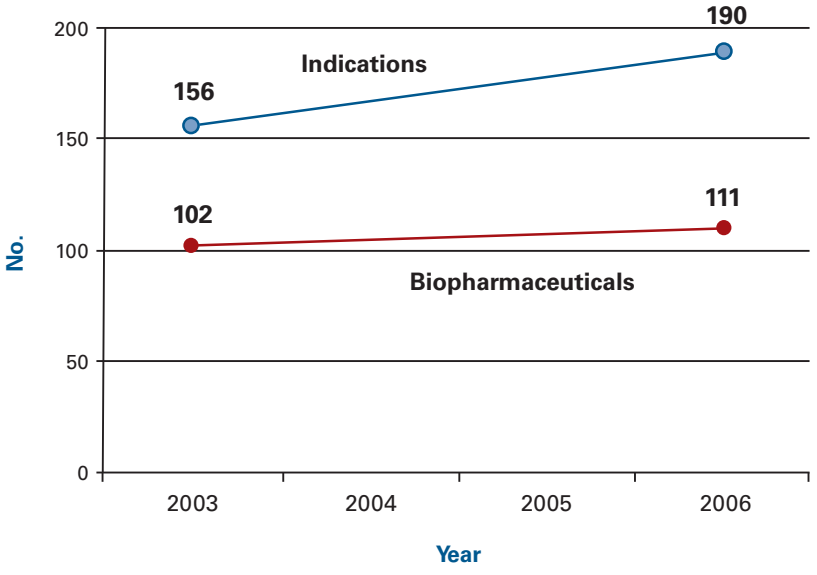
More than 90% of the biopharmaceuticals (and approximately 94% of target

Table. Disease Targets in 2006 and 2007*

Target	Biopharmaceuticals† (n = 111)	Indications (n = 190)
Cancer	43 (38.7)	83 (43.7)
Blood disorder	12 (10.8)	13 (6.8)
Rheumatoid arthritis	8 (7.2)	11 (5.8)
Type 1 diabetes mellitus	6 (5.4)	8 (4.2)
Crohn's disease	5 (4.5)	5 (2.6)
Psoriasis	5 (4.5)	5 (2.6)
Hepatitis C	4 (3.6)	4 (2.1)
Thrombosis	3 (2.7)	5 (2.6)
Systemic lupus erythematosus	3 (2.7)	4 (2.1)
Cardiovascular disease	3 (2.7)	3 (1.6)
Growth disorders	3 (2.7)	3 (1.6)
Infection	3 (2.7)	3 (1.6)
Multiple sclerosis	3 (2.7)	3 (1.6)
Pulmonary disease	3 (2.7)	3 (1.6)
Osteoporosis	2 (1.8)	4 (2.1)
Human papilloma virus	2 (1.8)	3 (1.6)
Ankylosing spondylitis	2 (1.8)	2 (1.1)
Bleeding	2 (1.8)	2 (1.1)
Diabetes-related complications	2 (1.8)	2 (1.1)
Dupuytren's contreature	2 (1.8)	2 (1.1)
Human immunodeficiency virus–related complications	2 (1.8)	2 (1.1)
Other genetic disorders	2 (1.8)	2 (1.1)
Vasculitis	2 (1.8)	2 (1.1)
Respiratory syncytial virus	1 (0.9)	2 (1.1)
Acne	1 (0.9)	1 (1.1)
Chronic fatigue	1 (0.9)	1 (1.1)
Dental-related disease	1 (0.9)	1 (1.1)
Gout	1 (0.9)	1 (1.1)
Hepatitis B	1 (0.9)	1 (1.1)
Human immunodeficiency virus	1 (0.9)	1 (1.1)
Immunodeficiency	1 (0.9)	1 (1.1)
Macular degeneration	1 (0.9)	1 (1.1)
Osteoarthritis	1 (0.9)	1 (1.1)
Short bowel syndrome	1 (0.9)	1 (1.1)
Stroke	1 (0.9)	1 (1.1)
Transplantation	1 (0.9)	1 (1.1)
Ulcerative colitis	1 (0.9)	1 (1.1)
Xeroderma pigmentosum	1 (0.9)	1 (1.1)

*Data are given as number (percentage).
†Biopharmaceuticals targeting more than 1 disease are counted once for each disease.

Figure. Agents and Indications in the Biopharmaceutical Pipeline



indications) would require administration via injection or infusion, and more than 70% of agents (approximately 73% of indications) will require administration by a healthcare provider, based on route and frequency of administration and duration of therapy. Almost 80% of the indications in the pipeline will require long-term (chronic) treatment (defined as >1 year). More than one half of those agents requiring administration by a healthcare provider are cancer related. Approximately 30% of agents are likely to be administered by the patient or a caregiver.

More than one third (38%) of agents in the pipeline will require intravenous administration. More than 40% of the subcutaneous agents in the pipeline are likely to require administration by a healthcare provider.

Late-stage biopharmaceuticals will affect at least 33 distinct physician specialties. Outside of hematology and oncology, the specialties that will be most affected are rheumatology, endocrinology, gastroenterology, and primary care. Agents and indications that require intravenous administration would affect more than one half of specialties.

Trends between 2003 and 2006 in agents and indications were analyzed by absolute number and by the proportion of the pipeline they represent. The pipeline is growing in agents and in indications (**Figure**). However, the number of agents increased by only 9% (from 102 to 111) from 2003 to 2006, whereas the number of indications increased by 22% (from 156 to 190).

Although the number and percentage of already FDA-approved biopharmaceuticals in the pipeline have not changed significantly, the number of indications they represent and the percentage of pipeline indications represented by these agents increased from 37 indications in 2003 (24% of pipeline indications) to 70 indications in 2006 (37% of pipeline indications), which is an 89% increase in indications and a 54% increase in the proportion of the pipeline. In addition, there is a greater percentage of "follow-on" indications in the pipeline in 2006 compared with 2003.

There is an increase in the number of agents and indications targeting cancer. In 2003, there were 30 cancer-related biopharmaceuticals (29% of pipeline agents) in late-stage development for 62 indications (40% of pipeline indications), while in 2006 there were 43 biopharmaceuticals (39% of pipeline agents) for 83 indications (44% of pipeline indications). In addition, the gap between cancer and other disease targets in the pipeline is widening. The second most common disease targets were infection in 2003 and blood disorders in 2006. There were 21 more cancer-related agents (21% of pipeline agents) than infection-related agents in 2003 versus 31 more cancer-related agents (28% of pipeline agents) than blood disorder agents in 2006 (an increase in the gap of 48%).

DISCUSSION

The biopharmaceutical pipeline continues to grow and will affect clinical decision making, benefit design, care access and care management, specialty pharmacy, and budget decisions. Three findings are particularly noteworthy. First, the breadth of agents' indications is expanding. The number of indications per agent was 1.5 in 2003 versus 1.7 in 2006. Twenty-five FDA-approved agents represented 37 indications in 2003, or 24% of the indications under development. In this study, 24 agents represent 70 indications, or 37% of pipeline indications. During 3 years, the number of secondary indications has increased substantially and represents a higher percentage of the pipeline overall. In addition, a large number of agents have been tested in completed phase 3 clinical trials. Each of these findings suggests a more rapid entry to market. Second, the number of agents in the pipeline that will require administration by healthcare providers is increasing, even agents that will have a subcutaneous route of administration. This finding has obvious implications for healthcare budgets and the develop-

ment of care management programs. Third, cancer was and remains the key focus of the biopharmaceutical pipeline. Six of 8 cancer-related biopharmaceuticals that have the most indications under development are already FDA approved for other indications, and the 2 top anticancer agents in the world (by sales) have multiple indications under development in the late-stage pipeline. These 2 agents have worldwide sales of more than $6 billion and US sales of more than $4 billion[1] (2006). The additional estimated US sales opportunity (over current sales) for these 2 agents is more than $7 billion.[6-8] Paradoxically, cancer is widely considered to be the least managed disease category by third-party payers.

The biopharmaceutical pipeline remains robust and growing, resulting in the ongoing introduction of new biologic agents into the marketplace. An understanding of the pipeline and the resulting market effect may help payers proactively prepare and create the framework for appropriate use.

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Take-away Points

The US biopharmaceutical pipeline is growing at an aggressive rate (16%-30%), faster than the rate of growth observed for traditional "pharmaceuticals" (approximately 4%). What does this mean to stakeholders?

- More patients and beneficiaries will experience increased survival, halting of disease progression, improved quality of life, and reduction in disability.
- Because biologics remain costly, the cost burden on the payer community will continue to grow.
- The near-term solution? Partnerships are needed between manufacturer, physician, and payer that focus on the clear-cut demonstration of clinical and economic outcomes–based value in the context of the real-world practice of medicine.

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