

Recombinant protein therapeutics—success rates, market trends and values to 2010

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Despite entering its maturation phase, the recombinant protein sector will continue to drive the growth of medical biotechnology over the next six years.

Biotechnology, founded on the principles of recombinant DNA (rDNA) protein production, is and will probably continue to be an R&D-intensive sector. Beginning in the early 1970s, advances in molecular biology and genetic engineering have led to enormous progress in the ability to understand the biomolecular roots of human disease. Stanford University's Paul Berg, the 1980 Nobel Prize winner in chemistry, first produced rDNA in 1972. His lead was followed by a team led by Herbert Boyer (University of California, San Francisco), who in 1973 transformed *Escherichia coli* cells with recombinant plasmid and later founded Genetic Engineering Technology (Genentech, S. San Francisco, CA, USA). Boyer's team perfected their methods, then developed and later launched, with the help of their licensing partner Eli Lilly (Indianapolis, IN, USA), the first human recombinant protein, recombinant human insulin (Humulin) in 1982. After more than two decades of continuous global expansion, business formation and technological diversification, the rDNA therapeutics sector now represents the core of the human medical biotechnology industry, worth over \$32 billion in 2003. The rDNA therapeutics sector includes more than 110 companies that are involved in the discovery, development and marketing of rDNA products. These companies have a pipeline of more than 80 therapeutics in clinical development and a combined

portfolio of 73 marketed products^{1,2}.

The analysis of the rDNA protein sector presented here discloses key trends that have guided the current market formation and that will affect future market growth. Our analysis included a thorough evaluation of the sector's historical approval success rates, followed by market analysis and revenue forecasts for the current key companies, therapeutic foci and leading protein classes. Only novel rDNA therapeutic products were evaluated; variants of innovative recombinant products (e.g., reformulations) and rDNA products developed as therapeutic vaccines were excluded. Therapeutic monoclonal antibodies were also excluded; success rates and market values for these products have been published³⁻⁵.

We find that, as the biotechnology industry developed and early rDNA products fulfilled their promise in the market, the resulting growth of the rDNA market guided the formation and composition of the current pipeline of products. Analysis of key trends relating to approved and pipeline products reveals that the current leading rDNA therapeutics will continue to dominate the market, and that pipeline products might have difficulty finding more than a niche.

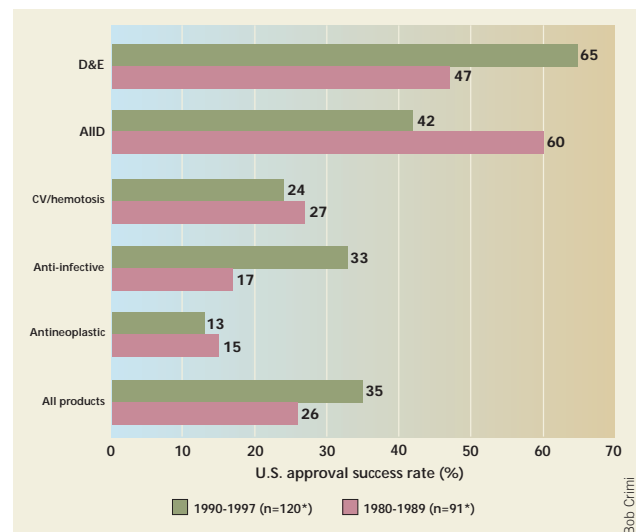


Figure 1 US approval success rates for rDNA therapeutics in two periods. *Total number of products that entered clinical study during period. AIID, arthritis, inflammation and immune disorders; CV, cardiovascular; D&E, diabetes and endocrinology. Source: Tufts Center for the Study of Drug Development.

That was then—the 1980s

The development of methods to manipulate DNA opened the door to virtually unlimited possibilities for recombinant protein production. In theory, the only limit was imagination. In practice, the prevailing biological knowledge and projected market size for rDNA therapeutics dictated the focus of early efforts. The proteins studied in the clinic in the 1980s were those that succumbed to the production techniques (e.g., restriction enzymes, cell lines) available at the time. The result was sometimes a protein without a clear therapeutic use (that is, a product in search of a disease) but could also be a protein of obvi-

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ous value (such as a recombinant version of an approved biologic).

In terms of the number of rDNA products, the interferon and interleukin therapeutics led the charge into the clinic. These proteins accounted for more than 30% of the protein therapeutics in clinical study during the 1980s. At the outset, the biological basis for efficacy of the products was unclear. Hence, decisions regarding the design of clinical studies (such as exact patient population, dosing, timing of dose) were challenging. Interferons and interleukins are pleiotropic agents (they cause a variety of effects), so the therapeutics were studied in a wide variety of diseases, including anti-infective, antineoplastic and immunological indications. Of the two cytokines, the interferons proved to be more successful. Six versions of interferon- α , - β , and - γ that entered study in the 1980s ultimately gained approval in the United States for chronic hepatitis C infection, hairy cell leukemia, chronic granulomatous disease and multiple sclerosis.

Human growth hormone (hGH) and insulin, both well-studied therapeutics with approved biologic counterparts, were early targeted for recombinant production because of the ease of production and large markets for these products. Versions of the two therapeutics made up nearly 15% of the total number of rDNA products studied in the clinic during this period. The obvious value of the market for hGH and insulin engendered participation by many companies in the race

to develop these products but also assured conflicts over intellectual property and marketing exclusivity. For example, although six versions of hGH were ultimately approved, legal and regulatory considerations kept most of the follow-on products off the US market for years.

Overall, rDNA therapeutics that entered clinical study during the 1980s had a 26% US approval success rate (Fig. 1). Products were studied mainly in five therapeutic categories, although nearly three-quarters of the rDNA therapeutics were studied in only three of these: cardiovascular-hemostasis (30%), antineoplastic (22%), and diabetes and endocrinology (D&E; 20%). A dozen were investigated as anti-infectives (13%); only five entered trials as arthritis, inflammation and immune disorders (AIID) agents. Of the therapeutics included in the 1980s cohort, all US approvals were in these five categories. A few products were also studied in enzyme therapy, ophthalmic and wound healing indications.

Therapeutics studied as antineoplastic agents were least successful; primarily, these products were versions of interleukin-1, -2,

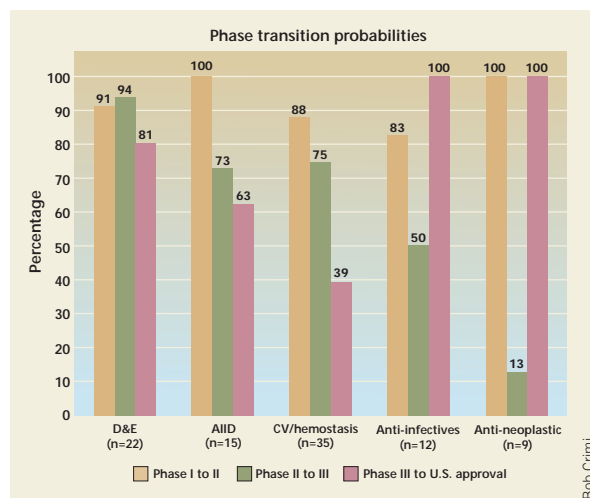


Figure 2 Phase transition probabilities by therapeutic category for rDNA products entering clinical study during 1990–1997. (See Box 2 for methodology.) AIID, arthritis, inflammation and immune disorders; CV, cardiovascular; D&E, diabetes and endocrinology. Source: Tufts Center for the Study of Drug Development.

and -4, and interferon- α and - γ . Investigation of cytokines in other indications ultimately led to the finding of efficacy in two immunological indications—multiple sclerosis and chronic granulomatous disease. This fortuitous discovery accounts for the high success rate (60%) for this category (AIID) of rDNA therapeutics.

The anti-infective and D&E categories were composed of several versions of only a few products. Interferons and versions of CD4 protein composed 83% of the anti-infectives. The majority of these therapeutics were studied as antivirals (for example, as treatments for AIDS, hepatitis C or herpes) but had a low US success rate (17%) compared with the entire cohort. Versions of hGH, insulin and insulin-like growth factor made up 89% of the D&E category. Eight variants of hGH and insulin were ultimately approved; thus, the category had a relatively high (47%) US approval success rate. The cardiovascular-hemostasis category included a more diverse set of products (for example, thrombolytics, clotting factors, blood cell production stimulants) and had a 27% US approval success rate.

Exploring new options from 1990 to 1997

As molecular biology techniques and medical knowledge advanced in the 1990s, the number and variety of rDNA therapeutics entering clinical study increased. Compared with the 1980s, 32% more products and therapeutics for three additional categories were first investigated during 1990–1997. This 8-year time frame was selected for comparison with

Box 1 Analysis criteria

Success rates and clinical phase transition probabilities were calculated for a cohort of 285 recombinant protein therapeutics sponsored in clinical study during 1980–2003 by US-based companies or by multinational companies that received FDA approval for rDNA therapeutics. Data were collected from surveys of the sponsoring companies and from public databases and documents. Records were updated through August 2004.

Approval success calculations were based on products with a known fate (US approval or discontinuation). Products launched only in non-US markets were considered to be discontinued in the US. Phase transition probabilities were calculated as follows: the number of products that completed a given phase (e.g., phase 1) and entered the next (e.g., phase 2) was divided by the difference between the number of products that entered the phase and those that were still in the phase at the time of the calculation.

The therapeutic category for an rDNA therapeutic was determined by, in decreasing priority order, the category of first approval, the category studied in the most advanced phase or the category in which the most studies were done. The cardiovascular-hemostasis category includes products that stimulate the production of blood cells (such as erythropoietin). The arthritis, inflammation and immune disorders (AIID) category includes treatments for diseases characterized by defects of the immune system that are not currently accepted as having an infectious causative agent (e.g., multiple sclerosis, chronic granulomatous disease, rheumatoid arthritis, Crohn's disease). Market values for multiple sclerosis therapeutics were presented separately in the central nervous system (CNS) category because of the large value of the markets.

the cohort in studies during the 1980s because, on average, the clinical development phase for rDNA therapeutics is 5–6 years. Therefore, a reasonable amount of time has now passed (that is, the 6.5 years from 1998 to mid-2004) for determination of the fates of the products. However, 19% of the products remain in clinical study, so the calculated success rates might change somewhat as the fates of these products are decided. In contrast, only 2% of the 1980s cohort is still in the clinic.

The number of products in nearly all the therapeutic categories increased during 1990–1997. The exceptions were the anti-infective and antineoplastic categories. The flagging interest was undoubtedly due to the low return on the investments made in these categories in the 1980s. In addition, the therapeutic focus during 1990–1997 was wider compared with the 1980s. The cardiovascular-hemostasis and D&E categories remained high priorities and composed 29% and 18%, respectively, of the total number of investigational products. Nine other categories each made up 12% or less of the total: AIID (12%), anti-infective (10%), antineoplastic (7%), neuropharmacological (6%), enzyme therapy (5%), wound healing (4%), respiratory (3%), bone-cartilage (3%). In addition, therapeutic rDNA treatments for indications in the neuropharmacological, respiratory and bone-cartilage categories (e.g., amyotrophic lateral sclerosis, cystic fibrosis, bone repair) were first studied in the 1990–1997 period.

Overall, US success rates for the 1990–1997 cohort were 35%, higher when compared with the 1980s cohort (Fig. 1), a result largely due to increases in the rates for the D&E and anti-infective categories. The overall rate was also buoyed by approvals in four categories not represented in the earlier time period: wound healing, enzyme therapy, respiratory and bone-cartilage. Success in these new categories demonstrates that the expanded focus of development programs in the 1990s relative to the 1980s was well worth the investment.

The probabilities of advancing through the various clinical and regulatory phases refine the profile revealed by success rates for the five main therapeutic categories of the 1990–1997 cohort (Fig. 2 and Box 1). Products must make four major transitions to successfully navigate the development and approval process: phase 1 to 2 transition when safety has been demonstrated, phase 2 to 3 transition when a product shows evidence of preliminary efficacy, phase 3 to regulatory review transition when efficacy has been demonstrated, and review to approval when FDA concludes that the product is suitable for patients. All products that underwent FDA regulatory review for indications in the

Box 2 Market analysis and forecasting methodology

To estimate market growth and revenues, Datamonitor uses its internally created econometrics model to calculate market growth. The forecast revenues of each therapy area are based on forecasts of individual products within each therapy area. Individual forecasts are made for the chief marketed products, including the largest products within the therapy area and any newly launched products with high growth potential. In addition, revenues from any products in R&D that are likely to be launched before 2010 within each therapy area are forecast individually.

To forecast individual products, specific growth curves are fitted to historical sales figures. The baseline forecast is then modified where appropriate to produce a final forecast of individual product sales. The size of the modification depends on the impact that specific events are forecast to have on the drug's overall annual revenues. To validate these forecasts, forecasts from previous years are reviewed and compared against actual revenues. To forecast products currently under clinical development, first-year sales are predicted by identifying a series of attributes that will contribute to the initial market share, and the product is then scored on each of these attributes. To strengthen further the validity of Datamonitor's impact factors, extensive primary research (focusing on innovation and comparative business model evaluation) extracted from a wide global network of academic, clinical medicine and industrial experts is also used to feed the forecasting engine.

five main categories did so successfully (that is, FDA review to approval phase transition was 100%), and so this transition was combined with the phase 3 to FDA review transition in Figure 2. Phase transition probabilities for the D&E, AIID and anti-infective categories were all 50% or greater. In contrast, the probability of moving out of phase 3 successfully was less than 40% for the cardiovascular-hemostasis therapeutics, and products in the antineoplastic category had a remarkably low phase 2 to phase 3 transition probability (13%), although the one product, denileukin difitox (Ontak; Ligand Pharmaceuticals, San Diego, CA, USA), a cytotoxic fusion protein with diphtheria toxin fragments fused to interleukin-1 that successfully completed phase 3 was approved.

This is now, 1998–2003

The variety of products composing the 1998–2003 cohort is similar to that of the 1990–1997 cohort, although the average number that entered clinical study per year is somewhat lower. Approximately 12 rDNA therapeutics were first tested in humans per year during 1998–2003, compared with 15 per year for the 1990–1997 cohort. Similar therapeutic categories are under study, although no products have been studied for neuropharmacological indications. Results from the 1990–1997 cohort of rDNA therapeutics in this category have not as yet been encouraging, so industry resources are perhaps being directed to more likely prospects.

The vast majority (79%) of the 1998–2003 cohort are in clinical study, so the accuracy

of success rates calculated now for this group would be questionable. However, predictions of the number of possible approvals can be made on the basis of success rates calculated for the 1990–1997 cohort. Projections based on either the overall success rate or the therapeutic category success rates indicate that 25 therapeutics of the 1998–2003 cohort might ultimately be approved in the United States. In addition, because 19% of the 1990–1997 cohort is still in clinical study, some of these products might also be approved in the future. Based on an approval success rate of 35%, an additional eight rDNA therapeutics from the 1990–1997 cohort might be approved. Several caveats must be noted: the exact time frame for all 33 predicted approvals is unknown, and the exact number approved might differ if the success rate for the 1998–2003 cohort differs from the success rate of the 1990–1997 cohort.

In the near term, the number of therapeutic rDNA approvals per year in the United States might be lower than those seen in the recent past. A total of five new rDNA therapeutics were approved in 2000, with six approved in 2001, five approved in 2002 and four approved in 2003 (ref. 2). In contrast, only two rDNA products, insulin glulisine (Apidra; Sanofi-Aventis, Strasbourg, France) and the fertility drug, lutropin alfa (Luveteris; Serono, Geneva, Switzerland), have been approved so far in 2004. As of October 2004, only three products—insulin detemir (Latus; Novo Nordisk, Bagsvaerd, Denmark), calcitonin, for treating osteoporosis (Unigene Laboratories, Fairfield, NJ, USA,) and palifermin, a keratinocyte growth factor used

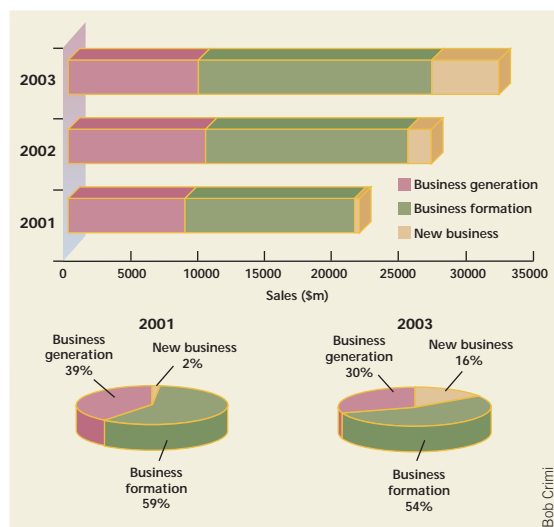


Figure 3 Market growth generated by three business waves and recorded between 2001 and 2003. Business generation: revenues generated by products approved before 1990; business formation: revenues generated by products approved between 1990 and 1999; new business: revenue generated by products approved between 2000 and 2003. Source: Datamonitor and company-reported information.

of total market size. Epoetin alfa (Procrit; Johnson and Johnson, New Brunswick, NJ, USA) was the top-selling protein, with sales of \$3,430m in 2001, \$4,269m in 2002 and \$3,986m in 2003, while the product's total market share in 2003 was 12%. Amgen's epoetin alfa (Epogen) was the second most important revenue earner, with 2003 sales of \$2,435m and a market share of 8%, followed by NovoNordisk's insulin (Novolin), with 2003 sales of \$2,235m and a 7% market share. Overall, Amgen's blockbusters managed to capture almost one-fourth of the market in 2003, with more than \$7,802m in total sales, showing the company's leading role in the rDNA market.

When looking at key geographic trends in 2003, the leading US biotech sector (Amgen and Biogen IDEC, Cambridge, MA, USA) captured a 28% market share but was closely followed by the leading US pharma players (Johnson & Johnson, Eli Lilly, and Schering Plough, Kenilworth, NJ, USA), which captured a 27% market share. In addition, the two leading European pharma players (Novo Nordisk and Roche, Basel, Switzerland) captured a 20%

in treating mucositis (Amgen, Woodland Hills, CA USA)—were undergoing FDA review.

Market size growth from 2001 to 2003

Working from extensive primary and secondary market research, the rDNA therapeutics' market growth between 2001 (the first year of the new century) and 2003 (most recent year with complete sales data) was calculated by Datamonitor Healthcare as part of an ongoing effort to track the sector's growth (see Box 2 for explanation of methodology). These calculations provide a baseline for future comparison with additional periods in the first decade of the 21st century. The market has developed as the biotechnology industry has evolved through three periods of economic growth: *business generation* (1980–1989, including the first decade of rDNA therapeutics approvals), *business formation* (1990–1999, with approvals signaling the sector's confident growth and maturation) and *new business* (including all new product approvals between 2000 and 2003).

The rDNA market grew from \$21,470m in 2001 to \$26,935m in 2002 and \$32,065m in 2003 (Fig. 3), while revenue growth rate fell from 26% between 2001 and 2002 to 19% between 2002 and 2003. Although the business generation wave saw its income growing by 19% between 2001 and 2002 from \$8,402m to \$9,993m, its revenue declined between 2002 and 2003 by 5% to \$9,525m, indicating signs of maturation and market saturation. Revenues generated by the sector's business formation wave grew from \$12,714m in 2001 to \$15,126m in 2002 and \$17,513m in 2003. In addition, new business revenues increased from \$354m in 2001 to \$1,816m in 2002 and \$5,027m in 2003, while its contribution to total market size grew substantially from 2% in 2001 to 16% in 2003.

Leading products and winning players

Ten leading products drove market growth between 2001 and 2003 (Table 1). Specifically, the ten leading products saw their sales increasing from \$12,923m in 2001 to \$16,102m in 2002 and \$18,362m in 2003, capturing 57%

Table 1 Top ten recombinant therapeutic proteins and their global sales between 2001 and 2003

Product (generic)/marketing company	2001 (\$million)	2002 (\$million)	2003 (\$million)	Growth (decline) 2002–2003 (%)
Procrit (epoetin alfa)/Johnson & Johnson	3,430	4,269	3,986	(6.6)
Epogen (epoetin alfa)/Amgen	2,108	2,261	2,435	7.7
Neupogen (filgrastim)/Amgen	1,346	1,380	1,268	(8.1)
Neulasta (pegfilgrastim)/Amgen	0	464	1,255	170.5
Novolin (insulin systemic)/Novo Nordisk	2,244	2,255	2,235	(0.9)
Avonex (interferon beta-1a)/Biogen IDEC	971	1,034	1,170	13.2
PEG-Intron A franchise (pegylated interferon alpha)/Schering Plough	1,447	2,736	1,851	(32.3)
Enbrel (etanercept)/Amgen	856	521	1,300	149.5
Aranesp (darbepoetin alfa)/Amgen	42	416	1,544	271.2
NeoRecormon (epoetin-beta)/Roche	479	766	1,318	72.1
<i>Top ten product sales</i>	<i>12,923</i>	<i>16,102</i>	<i>18,362</i>	<i>14.0</i>
<i>Others</i>	<i>8,547</i>	<i>10,833</i>	<i>13,703</i>	<i>26.5</i>
<i>Total market value</i>	<i>21,470</i>	<i>26,935</i>	<i>32,065</i>	<i>19.0</i>

Source: Datamonitor and company-reported information.

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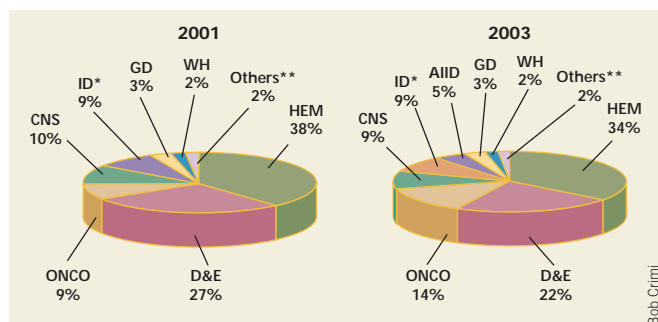


Figure 4 Therapeutic market segmentation from 2001 to 2003. AIID, Arthritis, inflammation and immune disorders; CNS, central neural system; D&E, diabetes and endocrinology; GD, genetic disorders; HEM, hematology; ID*, infectious diseases including HIV; ONCO, oncology; Others**, respiratory plus cardiovascular; WH, women's health. Source: Datamonitor and company report information.

market share. Overall, revenues generated by US firms in 2003 represented 65% of the market, while European and Australasian firms followed with 32% and 3%, respectively.

Therapeutic market segmentation

Analysis of therapeutic market segmentation from 2001 to 2003 reveals five therapy areas that were the key market shareholders (Fig. 4). These included hematology, D&E, oncology, central nervous system (CNS) diseases and infectious diseases (including HIV). More specifically, hematology (including mainly erythropoietins) saw its sales increasing from \$8,296m in 2001 to \$10,213m in 2002 and \$11,243m in 2003 with a 14% growth between 2002 and 2003, capturing 34% of the market. This was followed by D&E, which also saw its sales increasing from \$5,856m in 2001 to \$6,475m in 2002 and \$7,210m in 2003, with a growth rate of 13% between 2002 and 2003. On the other hand, oncology showed one of the strongest revenue growth rates between 2002 and 2003, with its sales and market share increasing from \$1,841m and 9% in 2001 to \$4,436m and 14%, respectively. Overall, the combined market share of the three main therapy areas decreased slightly, from 74% in 2001 to 70% in 2003. This market share decline is the result of the capture by AIID of a 5% market share in 2003.

Three leading protein classes—erythropoietins, interferons and insulins—led revenue generation for the period 2001–2003. Specifically, sales of the leading class of erythropoietins increased from \$6,211m in 2001 to \$7,868m in 2002 and \$9,466m in 2003, with a 2002–2003 growth rate of 20%, due in part to expansion in the oncology markets. In addition, the class of interferons saw its sales growing from \$3,900m in 2001 to \$5,427m in 2002 and \$5,473m in 2003, while its market share

declined slightly from 18% in 2001 to 17% in 2003. Similarly, the insulin market share dropped from 20% in 2001 to 17% in 2003, while class sales grew from \$4,257m in 2001 to \$4,745m in 2002 and \$5,357m in 2003. Overall, the three leading protein classes captured a 63% market share in 2003, which was a 3% decline from 2001. The latter trend is explained by the spectacular rise of

Global market growth from 2004 to 2010

Datamonitor Healthcare's discussions with biotechnology and pharmaceutical executives have revealed that the future growth of the rDNA market will remain the chief contributor to the industry's global economic prosperity, followed by the sectors of therapeutic antibodies, vaccines, DNA-RNA synthetics, small molecules, gene and cell therapies. Therefore, demonstrating the growth potential of the rDNA market (the core sector of the medical biotech sector) over the next 6 years, focusing on the revenue performance of the sector's leading players, key therapy areas and classes is very important. The extracted trends and market segment values might help the industry's managers to shape successful corporate growth strategies.

Leading products

Twelve brands will lead market growth over the next 6 years (Fig. 5). The group of the leading brands

will see its sales growing from \$19,674m in 2004 to \$29,669m in 2010, capturing 57% of total market size.

Four Amgen products will be the sector's leaders: its arthritis drug etanercept (Enbrel), pegfilgrastim (Neulasta), darbepoetin alfa (Aranesp) and Epogen. More specifically, Enbrel will be the sector's top-selling product with its revenues forecast to increase from \$1,820m in 2004 to \$4,458m in 2010 and an 8% total market share or 14% of the income generated by the 12 leading brands. Enbrel will be followed by another two Amgen products: Aranesp, which is expected to reach sales of \$3,818m in 2010, and Neulasta, with forecast sales of \$3,424m in 2010.

Leading players and their contribution to market growth

The period 2004–2010 will see the market's value growing from \$34,807m in 2004 to \$52,150m in 2010. Amgen is and will probably remain the undisputable market leader, in that it will see its share increasing from 26% in 2004 to 31% in 2010, with sales from its rDNA therapeutics forecast to grow from \$9,066m in 2004 to \$16,251m in 2010. Amgen will be followed by two European pharma firms, Roche and Novo Nordisk, which will see their sales increasing from \$3,133m and

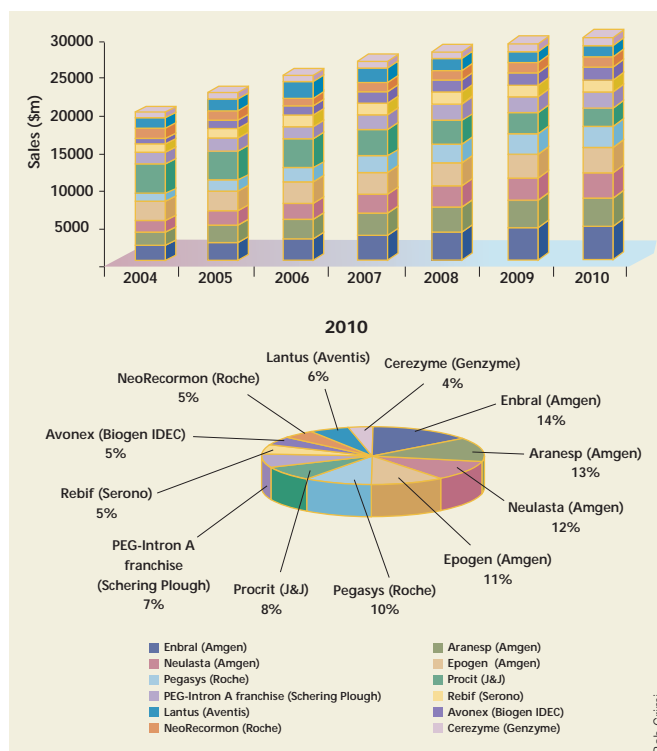


Figure 5 Distribution of market subsegments generated by the industry's leading recombinant protein brands within the 57% total market share in 2010. Source: Datamonitor and company-reported information.

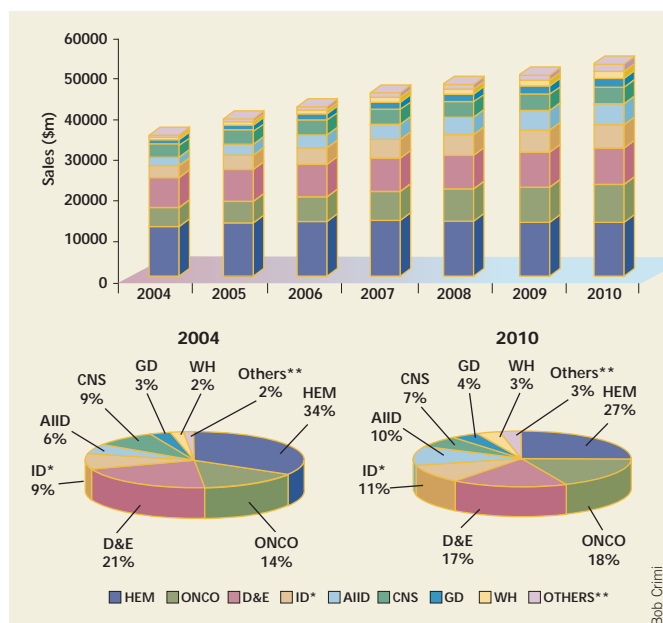


Figure 6 Market growth from 2004 to 2010. AIID, Arthritis, inflammation and immune disorders; CNS, central neural system; D&E, diabetes and endocrinology; GD, genetic disorders; HEM, hematology; ID*, infectious diseases including HIV; ONCO, oncology; Others**, respiratory plus cardiovascular; WH, women's health. Source: Datamonitor and company-reported information.

\$3,113m in 2004 to \$5,295m and \$3,512m in 2010, capturing 10% and 7% of the market, respectively. In terms of 2010 market capture, Johnson & Johnson will fall from second to fourth place, with its market share expected to fall from 12% in 2004 to 7% in 2010. In terms of market share capture, one of the emerging winners will be Serono. Sales generated by the rDNA business of the Swiss company, helped by the success of its interferon-β (Rebif in the US and EU multiple sclerosis markets) are forecast to almost double from \$1,859m in 2004 to \$3,110m in 2010, while its market share will grow from 5% to 6%, making Serono the second most important therapeutic protein biotech leader and the fifth global provider.

Although pharma players will continue to lead sales over the next 6 years, their annual revenue growth rate is expected to fall markedly from 9% in 2005 to no higher than 4% in 2010, while their market share will drop from 61% in 2004 to 48% in 2010, signaling a continuous and undisturbed period of business maturation. On the other hand, the role of the biotech sector—in terms of marketing independence and based on marketed portfolio and pipeline-driven revenues—will become increasingly important, because its market share is forecast to increase from 39% in 2004 to 48%, almost balancing the size of

pharma contribution to market growth in 2010.

Revenues generated by the sector's 73 marketed recombinant therapeutic proteins are forecast to grow from \$34,717m in 2004 to \$48,060m in 2010, for a market share of 92%. Revenues generated by pipeline products that might launch during 2004–2010 are thus expected to have a market share of only 8% by 2010, with sales forecast to reach \$4,090m. Over the next 6 years, income derived from the rDNA therapeutics that are currently in phase 2 will increase from \$80m in 2007 to \$539m in 2010. In addition, revenues

from products currently in phase 3 or registration will reach \$3,551m in 2010.

Evolution to 2010

Hematology will continue to lead sales over the next 6 years, with forecast revenues of \$12,007m in 2004 and \$13,409m in 2010 and a 27% total market share in 2010 (Fig. 6). Oncology will become the second most important revenue generator, with sales forecast to double from \$4,929m in 2004 to \$9,218m in 2010 and increasing market share from 14% to 18%. D&E will fall to second place, with almost flat sales growth and revenue forecasts of \$7,298m (21% of the market) in 2004 and \$8,935m in 2010 (17% of the market). AIID will be the most important emerging therapy area helped by Enbrel's success, with its marketing share forecast to increase from 6% in 2004 to 10% in 2010.

As for the future markets of the leading protein classes, erythropoietins will continue to lead sales with revenue forecasts of \$10,093m in 2004 and \$11,971m; however, their market share will fall from 30% to 24%. Interferons will follow, with sales expected to increase from \$5,903m in 2004 to \$8,901m in 2010, while their market shares will remain unchanged at 17%. Insulins will maintain their third place, with sales forecast to reach \$6,593m and a 13% market share in 2010. In addition, the class of

fusion-protein inhibitors (led by Enbrel) will see its sales almost tripled from \$2,299m in 2004 to \$6,366m in 2010, while its market shares will grow from 7% to 12%.

In the final analysis

The rDNA therapeutics market's value will continue to grow over the next 6 years from \$34,807m in 2004 to \$41,744m in 2006 and \$52,150m in 2010. Despite a predicted increase of up to 50% in the number of approved products, the market will also continue to rely more on 12 blockbusting brands (with a market share of no less than 58%) and less on the pipeline, because the latter will not be able to drive growth or generate more than \$4,000m (8% of the market) in 2010. During the same period, biotech firms that produce rDNA therapeutics will overtake big pharma peers in revenue contribution to total market size, signaling maturation of the biotech industry and an increased reluctance to relinquish control of valuable products. Of these biotech companies, Amgen will be the undisputable market leader, and its flagship product Enbrel will be the sector's leading brand. Hematology, the mature leading therapy area that includes Amgen's Epogen/ Aranesp and Johnson & Johnson's Procrit, will continue showing some signs of growth, ultimately representing almost one-third of market share in 2010.

To sustain growth during the next 6 years, the rDNA sector will attempt to continue investing in product life cycle management strategies, including new delivery methods for therapeutics and devices that are more patient-friendly. Technical advances, such as the introduction of inhalable insulins in the diabetes market or the application of pegylation techniques to prolong product activity in the human body, will be central in the sector's attempt to revive growth and continue introducing high-value products. The degree of success achieved will depend on effective intrasector (e.g. bio-to-bio) or intersector (bio-to-pharma) partnering, because the relevant technical advances and products might not be owned by the same company.

Acquisitions and mergers, both intrasector and intersector, will continue to play an important role in determining market share. For example, the \$16 billion acquisition of Immunex provided Amgen with Enbrel, the industry's new growth driver, and worked to revive investor confidence in the company. In addition, the acquisition of the emerging biotech player Scios by the US giant Johnson & Johnson shows that the acquisition of a biotech-originated drug, the heart medication nesiritide (Natrecor), a human natriuretic

peptide, by an experienced pharma player can offer higher returns.

The rDNA market could, in several key therapy areas such as oncology, CNS disease, infectious diseases and AIID, face strong competition from other technological platforms such as antibodies (e.g., Johnson & Johnson's Remicade or Abbott's Humira vs. Amgen's Enbrel in arthritis, Genentech's antibody Raptiva vs. Biogen IDEC's fusion protein Amevive in psoriasis) or small-molecule drugs (e.g., Teva's oral copaxone vs. Biogen's Avonex and Serono's Rebif). For this reason, companies may attempt to diversify risk by investing in new technological platforms. For example, the merger between Biogen and IDEC united a leading rDNA biotech specialist with an antibody expert and created a hybrid portfolio with blockbusters or strong income earners from two different technological platforms. Another example is the recent \$1.2 billion

acquisition of Tularik and its small-molecule pipeline by Amgen.

The entrance of biogenerics in the European and Asian markets could potentially hinder the sector's quest for sustainable growth. Biogenerics could give rise to pricing pressure for the currently branded products and might also push profit margins down. The situation in the United States is complicated because most rDNA therapeutics have been, and will continue to be, approved under the Public Health Service Act, legislation that has no provisions for approval of generic versions. A few rDNA therapeutics (such as insulin and hGH) are potentially eligible for production as generics, but the FDA has not accepted responsibility for approving these products. The question whether biogenerics will enter the US market thus remains open.

During the first decade of the 21st century, medical biotechnology will probably see its core sector of recombinant protein thera-

peutics maintaining sustainable growth and might avoid a war with biogenerics entrants. It remains to be seen how the forecast earnings will be used to secure another decade of economic prosperity. In our opinion, the new era of biotechnology will shift the focus from recombinant replacement therapies to novel biomolecular and synthetic structures that will be based on breakthroughs in molecular medicine and the decoding of the highly complex human genomics and proteomics maps.

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