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In vivo to *in vitro* to *in silico*:[1] Coping with Tidal Waves of Data at Biogen

By early 2002, Biogen was one of the few success stories in biotech. Founded in 1978, it had survived in a tough industry, one in which early starts often lead to mergers, no profits, and/or bankruptcies. By FY2001, Biogen sales had reached $1.0 billion dollars with a healthy $273 million in net income. Its market capitalization was approximately $8.2 billion.[2] R&D spending, at 30% of revenue, was among the highest rates in the industry. (See **Exhibits 1** and **2**.)

Yet Jim Mullen, Biogen's CEO, knew the company now faced another critical juncture. The world in which biotechnology companies operated had changed dramatically over the past few years. Various governments and companies had launched massive genomics projects to sequence, annotate and use gene data from viruses, bacteria, plants, animals, and humans.[3] Parts of biology were rapidly evolving from being an individualistic, wet lab, bench-science driven field towards one where scientists manipulated huge amounts of data and divided up research steps into a factory-like production process. At the same time, the cost of developing a drug and bringing it to market had ballooned, from an estimated $231 million in 1991 to $802 million in 2000.[4] This had led some to believe that scale economies in research and development would give large, well-funded competitors an advantage.

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[1] Biological research can be conducted *in vivo* that is on live animals or *in vitro* on tissue and cell cultures held in petri dishes. Now more and more preliminary research is carried out within computers that are *in silico* rather than in wet labs. "Wet" lab space refers to laboratory space equipped with benches, ventilation hoods, ventilated storage areas, sinks, lab equipment, etc. where "wet" experiments can be conducted safely. Such laboratory space is relatively expensive to build and maintain.

[2] "Biogen Delivers on Operating Earnings Guidance of $1.90 Per Share After One—Time Charges," *PR Newswire*, January 24, 2002.

[3] The first full complex genome sequenced was haemophilus influenzae (R.D. Fleisehmann, et al., "Whole-genome random sequencing and assembly of Haemophilus influenzae Rd," *Science*, vol. 269 (July 28, 1995): 496-512), this process culminated six years later with the simultaneous publication of two draft versions of the human genome. (J. Craig Venter, et al., "The Sequence of the Human Genome," *Science*, vol. 269: 1304-1351 (February 16, 2001), and The Genome International Sequencing Consortium, "Initial sequencing and analysis of the human genome," *Nature*, vol. 409: 860-921 (February 15, 2001)).

[4] Tufts Center for the Study of Drug Development, Press Release, Boston, Mass., November 30, 2001. The 1991 figure is expressed in 1987 dollars.

Research Associate Gaye L. Bok prepared this case under the supervision of Juan Enriquez, Director of the Harvard Business School's Life Science Project, and Professor Gary P. Pisano. HBS cases are developed solely as the basis for class discussion. Cases are not intended to serve as endorsements, sources of primary data, or illustrations of effective or ineffective management.

Major pharmaceutical companies had been consolidating for years, with the top ten firms accounting for 64% of pharmaceutical revenues in 2000, up from 58% in 1995.[5] Most, if not all, had acquired biotechnology firms to add to their quiver of drug development tools. They were also deploying ever more sophisticated IT modules and accessing databases much larger than any databases ever used previously in the industry. (See **Exhibit 3**.)

Potentially, pharmaceutical and biotech companies now faced increased competition from what had begun as gene sequencing-data companies. Start-ups like Millennium, HGS, and Celera had achieved billions in market capitalization and were attempting to integrate forward into the therapeutics market by leveraging their massive genomic databases. Even information-computer companies, such as IBM and Compaq, were targeting life sciences as a key area for future growth.[6]

For a while, Biogen ignored many of these trends. After all it had been successful; it had more than enough to focus its energy and budget on, and it was a leader in Multiple Sclerosis (MS) research. But by the late nineties, it was clear that the world of biology had changed radically and that Biogen needed to catch-up in utilizing bioinformatic tools and understanding rapidly accumulating gene databases. This realization led to a restructuring of its computer systems and lab research. Suddenly massive amounts of data began to flow into the company.

"You must understand," said Michael Rosenberg, Biogen's Associate Director, Bioinformatics, "a revolution (as to how we do research) occurred here at Biogen eleven or twelve months ago. It was generally well accepted, and long awaited, and we expect to see the impact on candidates in the Discovery, Validation and Pre-clinical. It is harder to foresee the impact on Phases one, two, and three."

Restructuring the first part of a drug development pipeline, that is target identification and development prior to pre-clinical evaluation, might also imply significant changes down the road for other parts of Biogen. As Jim Mullen thought about what his company might look like in five years, he asked himself what changes might be required within various parts of his organization including finance, human resources, lab architecture, and clinical trials. Did Biogen have the scale to implement these changes by itself? And, as Mullen surveyed the external competitive landscape, he also wondered who might become a critical ally and who a foe?

Great Lab Science Begets Biogen

Biogen was founded and grounded in a tradition of great lab science. The company was one of the first to develop recombinant proteins using genetic engineering technology.[7] Two of its co-founders, Phillip Sharp and Walter Gilbert, won Nobel Prizes. Inventors like Charles Weissmann and Sir Kenneth Murray built great labs and dreamed up new products. The overall ethos was to find superstars and build labs around their talents.

But great science does not automatically imply great business. Biogen circa 1985 resembled a big post-doc lab. There was a lot of interesting work on protein and molecule development. This work was then published, but there was little focus or follow up on developing commercially attractive

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[5] Derived from Pharmaceutical Companies sales data, Compustat Global Vantage.

[6] For a description of these trends see Juan Enriquez and Ray A. Goldberg, "Transforming Life, Transforming Business: The Life-Science Revolution," *Harvard Business Review* (March-April 2000), pp. 94-104.

[7] Walter Gilbert et al. Protein Secretion. July 6, 1982. USPTO Patent # 4,338,397.

products. For example, although Biogen filed a U.S. patent application for Recombinant DNA molecules and their use in producing human interferon-like peptides in 1980, the patent (# 4,530,901) was not issued until July 23, 1985. Even then, profits still seemed a distant promise. Beta Interferon was initially launched as a cancer drug, and failed. It was then pursued as a treatment for hepatitis with limited success, and only later was tried successfully against multiple sclerosis.

Wall Street became restless. Growing R&D expenditures on a broad range of projects led investors to question Biogen's commitment to turning a profit. In a bid to transform a research organization into a vertically integrated development, manufacturing, and marketing organization, the board recruited Jim Vincent to serve as CEO in 1985. He found that the company was close to a financial meltdown.[8] Vincent sold off Biogen's European operations, built up the management team, and renegotiated important royalties for the interferon products. He also refocused research on four areas: inflammation, thrombosis, virology and selected cancers. A number of products already in development were slashed and headcount reduced from 500 to 225 employees.[9] Over time, Vincent focused the company's product development efforts on two drug candidates, Hirulog (a blood thinning drug) and Avonex (then targeted at Hepatitis). Biogen became profitable in 1989.

As the two drugs progressed to Phase III clinical trials, Jim Vincent realized that Biogen had to add to its core competence and focused on bringing in a CEO with operating experience. He brought in James Tobin, from Baxter International, as President and COO in 1994. At that time, Hirulog was the favored project, but efficacy trials showed it was not that much better than the then market leader. At the same time a Biogen competitor, Chiron Corporation, was bringing a similar beta interferon to market for treating multiple sclerosis. Biogen's scientists recognized that their variant of beta interferon would outperform Chiron's. Management suspended trials of Avonex in hepatitis, brought forward their trials of Avonex in multiple sclerosis, and cut the Hirulog project in order to take Avonex to market quickly.[10] The gamble paid off. The product was a success and provided a rapidly rising stream of product revenues, enabling Biogen to remain profitable and grow.

Biogen's management had effectively bet the company on bringing one product, Avonex, an Interferon beta-1a to treat relapsing forms of multiple sclerosis, to market. Through innovative partnerships, Tobin was able to outsource drug formulation, packaging, warehousing and distribution, while retaining the critical bulk manufacturing operation in-house. This helped ensure a large supply and rapid distribution of Avonex.[11] In 1997, after the successful commercialization of the company's sole proprietary drug, Tobin was named CEO and asked to focus on increasing Biogen's drug pipeline.[12] During this period, Biogen initiated numerous partnerships to pursue new disease indications and tried to acquire early stage products.

However, in December 1998, Jim Tobin abruptly resigned citing personal reasons. Vincent once again stepped in as CEO and promoted Jim Mullen, the head of international operations, to President. Mullen had joined Biogen in 1989 after nine years at SmithKline-Beecham Corporation, and had come up through Biogen's operations organization, rising to Vice President, Operations in

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[8] See Steven C. Wheelwright, "Biogen Inc.: rBeta Interferon Manufacturing Process Development," HBS case No. 696-083. This covers the early history of the company.

[9] Lawrence M. Fisher, "The Rocky Road From Startup to Big-time Player: Biogen's Triumphs Against the Odds," *Strategy & Business* (third quarter 1997), Booz Allen & Hamilton, http://www.strategy-business.com/casestudy/97305/page1.html.

[10] Ibid., page3.html.

[11] David Bovet and Joseph Martha, "Biogen Unchained," *Harvard Business Review* (May 2000), p. 28.

[12] Ronald Rosenberg, "Biogen Engineers Leadership Change of Company," *The Boston Globe*, February 15, 1997.

December 1991 until 1996 when he was appointed Vice President, International.[13] An engineer by training, Mullen had succeeded by focusing on operations and getting things done. In May 2000, Mullen became CEO, while Vincent remained Chairman of the Board of Directors.

A Continued Quest to Diversify

Despite its financial success, Biogen was in a delicate position. It continued to live primarily off Avonex. In FY 2000, the drug accounted for $761 million, or 82% of Biogen revenues. (Biogen's other income derived primarily from royalties on worldwide sales of products it had licensed out in its early days, including alpha interferon and hepatitis B vaccines as well as diagnostic products.)[14] In January 2001, CEO Jim Mullen told the financial community: "Biogen's next great challenge is to transition from being a one-product company into a multi-product company."

Nevertheless, the company believed its marketing relationships with physicians specializing in M.S. was one of its key competitive advantages, and it sought to extend its coverage of the M.S. market (**Exhibits 4** and **5**). As of early 2002, nine of the 14 products undergoing clinical trials at Biogen were Avonex related product extensions.[15]

For much of its history Biogen had prided itself on the quality of its biology and relied on the opportunistic research culture, as well as partnerships, to bring drug candidates into the pipeline. Lab biologists and the medical division were the key drivers in deciding where Biogen should put its research efforts. This culture centered on strong individual scientists with small, independent laboratories. Success was determined by finding good target genes using crack scientists, "wet" lab space, creativity, and a great deal of luck. By definition, biology remains a set of incredibly complex systems. Interactions between living creatures and drug molecules are often unpredictable and hard to understand fully. As Victor Koteliansky, Biogen's Director of Biological Research put it, "In biology it is a rule of the game that on Monday your experiment is working and the same experiment on Friday gives you partially a different thing! "

Identifying the genes responsible for human diseases remains a difficult, labor-intensive process. Finding a promising target that a small molecule or protein could interact with to block a disease without causing excessive side effects typically consumed large portions of a biologists' career. Scientists would rely on library research and clinical studies to develop a hypothesis regarding what genes and proteins were implicated in a disease. Then they would begin arduous lab work to test their hypothesis. Target validation was unpredictable and very time consuming. Even after identifying genes, compounds had to be isolated and introduced to living organisms." Test cycles on bacteria and mice would be run and meticulously recorded, then a further battery of extensive animal tests would eventually lead to a few human trials.

Faced with these challenges, Biogen's management had been quite conservative in funding projects throughout the nineties. Many scientists felt that a cumbersome decision making process had stifled projects. Although researchers could pursue a breadth of good ideas, getting a go ahead required multiple presentations, first to the research management and then to Joe Davie, head of R&D, as well as to the directors of the Medical and Marketing departments, and ultimately to Jim Vincent.

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[13] Biogen, Inc., 10K, March 2001 (via Hoovers online).

[14] Biogen Annual Report, 2000.

[15] Biogen.com, Product Pipeline, January 24, 2002.

There were good reasons to be cautious. Developing therapeutic drugs remains a risky and expensive business (**Exhibit 6**). The Pharmaceutical Research and Manufacturers of America (PhRMA) trade group estimated that out of 5000 drugs that entered pre-clinical testing, only five would proceed to clinical trials.[16] Only one of these five clinical candidates would eventually reach the corner pharmacy.[17] Stringent tests and protocols, required by the Federal Drug Administration (FDA), meant it took twelve to fifteen years to bring a drug to market. Cost estimates for a new drug ranged from $500 million (PhRMA), to $802 million (Tufts Center for the Study of Drug Development), to even higher figures put forward by various consulting firms.[18]

Costs increase substantially throughout the clinical study phases, with the largest outlays occurring in Phase III, because a company must recruit thousands of people to test the drug. (See **Exhibit 7**.) Even after reaching Phase III, a significant number of candidates failed to demonstrate the efficacy and safety required to win FDA approval. This meant that companies had to invest in various failures and wait 12 to 15 years before having any hope of generating new revenues. Keeping a pipeline full of potential compounds at various development stages was critical to investor confidence. Despite these high hurdles, for large pharmaceutical companies, drug development remained a profitable investment.

Unfortunately, by the end of the nineties, much of Biogen's promising pipeline seemed to be drying up (**Exhibit 8**). Investor relations had a difficult time articulating Biogen's R&D strategy, and there was frequent confusion regarding how far along the development pipeline various projects were. In September 1999, a promising new drug, Antova, experienced safety issues during its Phase II evaluation. Trials were halted. Some on Wall Street came to believe that the pipeline was largely empty.

A New R&D Strategy

A strong focus on the bottom line and conservative attitude towards the technology had led senior management to turn down several opportunities to collaborate on leading-edge genomics projects. According to Rich Cate, Director, Gene Discovery, "We didn't make a big effort to get into the sequencing game. . . . We continued to make small decisions, to turn down opportunities as they arose, and eventually this came to be seen as a strategic decision."[19]

Meanwhile a revolution had occurred in the scale and detail of gene data available, and Biogen was not on board. Many of those involved in R&D, particularly those focusing on gene discovery, became increasingly frustrated with the Company's conservative approach. "There was a lot of data out there . . . we had to harness this information . . . and the use of it." Start-ups began trumping Biogen researchers; for instance, during 1997-1998 the company laboriously identified and cloned a receptor called RETL3. But while they were searching for its operating mechanism and binding site, they were beaten by Washington University and by a Copenhagen company, NsGene A/S. This

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[16] PhRMA as cited by Biogen, www.Biogen.com, January 24, 2002.

[17] Tufts Center for the Study of Drug Development, "Backgrounder: How New Drugs Move through the Development and Approval Process," November 30, 2001.

[18] These various estimates include the costs of pursuing failed candidates abandoned at various stages of the development process.

[19] Biogen was not entirely out of genomics. It had partly funded an academic research institute in Switzerland; Jurg Tschopp was developing good bioinformatic tools, particularly algorithms used to for searching for proteins.

consortium won because it had used bioinformatics, *in silico* biology, to speed discovery.[20] Biogen eventually signed a research collaboration with the Copenhagen company to develop a drug candidate, Neublastin, but NsGene retained the rights to central nervous system indications.

Mullen realized that the company had fallen way behind in informatics and genomics. Biogen had outsourced most gene expression analysis to a biotech start-up, Curagen, in 1997. Aside from a couple of young scientists poached from genomics companies, Biogen had little internal ability to access, interpret, and apply geometrically expanding gene research databases. As the information available about diseases and genes became overwhelming, Biogen was forced to retool. According to Rich Cate, "Even if we weren't going to launch a genomics effort at that point, we had to know what genes were out there to compete on a level playing field."

By 1999, Mullen had started to make some fundamental changes within the company. He spent time working with the Boston Consulting Group to develop a proactive R&D strategy. The objectives were threefold: to define what Biogen wanted its scientists to work on, ensure senior management understood what and why research was focused on certain projects, and align R&D investment with the company's business development targets.

Eventually the R&D team identified four key areas: immunology, neurodegeneration, cancer and fibrosis. Having established a set of priorities, it became easier for senior management to delegate and streamline R&D project approval, provided projects fell into one of the agreed areas. Joe Davie, Vice President of Research, led the effort initially; a team of scientists began to filter a long list of potential targets down to 93 diseases of possible interest to the company. Their triaging criteria were based on market attractiveness and Biogen's perceived competitive strengths. Each disease was then re-examined in an effort to figure out which underlying pathologies might maximize "disease reach".

The Hard Road from *in vitro* to *in silico* Biology

But before launching these new R&D efforts, the company had to restructure its information systems department (I.S.) and, more important, the attitude of both management and bench scientists towards computer aided research.

Through the late 1990s, one rarely saw PCs on senior executive desks. As is typical in many companies, the I.S. department reported to the Chief Financial Officer and researchers were viewed as secondary customers. This is because the initial use for I.S. was automating the payroll and updating budgets. A desire to keep older finance applications running meant that the company used a legacy system based on a single VAX machine. Year 2000 (Y2K) demands forced Biogen to abandon the old VAX system in favor of two UNIX servers with 8 and 10 CPUs respectively. (But even this significant increase in capacity paled in contrast to Millenium, a Biogen competitor that was estimated to have 180 CPU capacity.)[21] Biogen's two computers ran everything—Oracle databases, data queries, gene research, but there were no shared services between the two machines.

The absence of adequate information technology became a source of constant friction between R&D and I.S., particularly as biologists began to try and assemble a map of all the genes in various organisms. Even downloading on-line data was too much for this system; Biogen had to ask the

[20] Bioinformatics takes masses of gene and protein sequence data gathered from various life forms and then compares known gene functions, potential treatments, and biologically active binding sites. This data is sometimes complemented by combinatorial chemistry, which designs and tries millions of slightly different molecules.

[21] Interview with Michael Rosenberg, November 28, 2001.

government for custom sets of a dozen compact disks to upload data to its increasingly obsolete system. As Rich Cate noted, "Through the summer and fall of 1998 the public database information was updated so infrequently on the VAX that we were out of date often."

Whenever researchers had requested system upgrades or internet access, the finance division had applied typical financial system criteria to those requests. This often ignored the burgeoning genomics field and its strategic importance for drug candidate discovery. Meanwhile many companies entered into a gene sequencing competition, investing heavily in expensive equipment and building a bioinformatics capability. They were comparing entire sets of genes, and using rapid computing power and sophisticated algorithms to detect gene-based differences between diseased tissue and "normal" tissue.

By 1999, the strategic planning process made it clear that Research I.T. had to be upgraded and responsibilities shared. The company hired a genomics expert, Michael Gilman, who left his position as Executive Vice President and Chief Scientific Officer for ARIAD Pharmaceuticals. (Gilman had previously trained and worked for eight years at James Watson's Cold Spring Harbor Laboratory.)[22] Soon after, Rainer Fuchs was recruited from Aventis to establish a bioinformatics group. Fuchs' new area inherited a number of I.S. people and the few employees who had some bioinformatics / combinatorial chemistry experience. Fuchs also brought in six new employees. Eventually the group achieved responsibility for all R& D informatics decisions.[23]

The Bioinformatics group spent its first year building up R&D information systems and infrastructure. They created a separate Oracle database server and introduced typical application / development protocols. A Linux farm, put together with relatively inexpensive servers, increased processing capacity approximately tenfold.[24] This investment was a fraction of what it would have cost to buy a similar sized mainframe a couple of years earlier. Links to the internet were vastly increased. Michael Rosenberg, Associate Director, Bioinformatics, estimated that with its increased data processing capacity and 4 Terabytes of dedicated storage, Biogen could theoretically download the entire NCBI (Genbank public database) in one hour.[25]

In parallel, Biogen was also building up its biology-genomics tool kit. John McCoy was hired in an effort to upgrade Biogen's discovery process; he took over as vice president of discovery biology and set to work expanding the company's database access capabilities. After buying a $2 million Sun Microsystems package, he subscribed to Incyte's proprietary database. Then, he substantially upgraded its access and use of public databases.

Hiring bioinformaticians is not easy or cheap. A recent graduate with a Masters degree would sometimes cost as much as a Biogen Senior Scientist and also required providing a package of stock options. Even then, some chose a different company at the last minute. Nevertheless, in two years Biogen went from having two specialists in research informatics to twenty-five and expected to

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[22] Watson and Crick were the discoverers of DNA see: Watson, James and Francis Crick, "A Structure for Deoxyribose Nucleic Acid," *Nature,* April 2, 1953.

[23] This group retained a dotted line of responsibility to the new Chief Information Officer, a position established in 2000.

[24] Often biotech and genomics companies that require massive computing power chose to network powerful desk workstations rather than purchase a supercomputer.

[25] All publicly funded gene sequencing data is supposed to be deposited in a centralized public databases, within twenty-four hours. This data is supposed to be freely accessible. There are three key centers, one in Japan, on in the United States and one in Europe.

double this number over the next two years. The I.S. budget for R&D swelled to over $10 million per year.[26]

Tidal Waves of Data

As the company and its systems went both digital and genomic, researchers' access to and use of computers and data sets increased exponentially. Instead of controlling or Balkanizing computers, the Linux farm and databases were open to all researchers at Biogen. To put this change into context: after years of laborious genetic research, both in house and in partnership with Curagen, Biogen's internal database held about 200 proteins. Literally overnight, simply by subscribing to Incyte's database, Biogen's database expanded to 12,000 proteins.

Given a sixty-fold magnitude shift in data availability, a few scientists thrived, but many initially chose not to access the data. Even though all two hundred scientists reporting to the head of Research had access to the new information, only about 10% chose to get training in how to use it. Perhaps ten people became active users.[27] Those who were not on-line soon found themselves falling farther and farther behind. Those who did go on-line found that new information grew geometrically.

Research management tried to help researchers by developing a targeted "scouting" system. Rather than asking everyone to go fishing in overwhelming data pools, they asked everyone what genes, proteins, or targets they were looking for. Then, using a bioinformatics querying software package they built customized "sniffer" programs. These "bots" would search the enormous amount of data posted every night on public databases looking for matches with the company criteria. If they identified a "hit" this information was passed on to a scout, a scientist, who would follow up with additional preliminary analysis. If the information seemed valuable, then the particular researcher would get a summary, a site address, and relevant links. This approach, it was hoped, would ensure the advent of genomics at Biogen was firmly tied to market based objectives, and would not become an end to itself.

At first researchers were very happy. Searches that would have taken days or weeks were now automated and updated daily. For a few weeks everything seemed fine. Then a few e-mails began coming in from individual Biogen researchers. They all had a similar message; "we are overwhelmed, please shut the spigot." But this was not to be. It was merely the beginning of an onslaught of data, because Biogen was about to incorporate in-house gene profiling capability.

As Biogen's discovery-focused teams began developing experiments based on the reams of data flowing from public databases, they realized they had to expand their in-house expression-profiling lab massively. In late 2000, a former colleague of Fuchs' from Aventis, Steve Perrin, was hired to set up and run a gene expression-profiling lab within Biogen. This was a key tool in understanding why someone gets sick or stays healthy; various genes are expressed differentially, either up regulated or down regulated, in diseased tissue.

Obtaining and interpreting a gene expression profile used to be a complex and laborious process. Working with Curagen, Biogen scientists had been focusing on around one thousand genes that were differentially expressed in diseased tissues and healthy tissues. Biogen's scientists managed six to eight projects a year and had to wait three to six months for results.

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[26] Fuchs interview.

[27] Carulli interview.

But as Biogen upgraded its labs and began using gene chips manufactured by Affymetrix, the amount of data exploded. Each Affymetrix chip created around forty megabytes of data and about one million new data points. Given that an average experiment employed about one hundred chips, and that Biogen's new lab could do six major experiments every three months, scientists were suddenly faced with analyzing and trying to make sense of billions of new data points showing how genes react when cells are attacked by a disease. (Single, complex experiments could consume five hundred gene chips and generate half a billion data points.)

As the data yielded up masses of new targets, workflow within the molecular biology labs changed dramatically. Previously, a scientist would walk a potential medicine through the entire development process, becoming an expert on a particular gene, protein, and condition. A star scientist and his assistants "owned" a disease and the molecules used to attack it. Now lab work became so vast and overwhelming that the process of validation had to be broken down into discrete steps. Not everyone was happy with this change. As John Carulli, Senior Scientist, Discovery Biology, explained, "fifteen minutes of fame turns into fifteen seconds of fame. This has a real effect on people's morale."

As various specialized groups began moving large numbers of targets through a particular step or cluster of steps, speed increased, but there was less opportunity for cross training, particularly for lab associates, and fewer opportunities to distinguish oneself through excellent and creative lab work.

But there were also significant advantages to having complete data sets. John McCoy, Vice President of Biogen's Discovery Biology Department thought: "Before you had these large scale profiling technologies, people would tend to think in a one-dimensional way, looking at one gene at a time, coming up with a hypothesis, testing the hypothesis and refining it before jumping on to the next gene. Now at the beginning of an experiment you have the opportunity to look at everything. That's a totally different way of approaching the problem. You start with all the information, and then devise filters to get to an answer. There's a lot of filtering going on."

ERPs, PEPs, and CIPs . . .

A flood of opportunities now superseded Biogen's and Wall Street's original concern, a lack of targets in the pipeline. This meant that instead of carefully watching and nursing a few compounds along, the company would have to quickly and efficiently develop a system to triage masses of targets and compounds. Biogen built a "value chain" stage gating process, which established explicit criteria for product development. Targets went through three stages: Exploratory Research Projects (ERPs), Prospect Evaluation Projects (PEPs), and Candidate Identification Projects (CIPs) before passing to the "Pre-clinical" stage.

Teams within the ERP stage focused on discovering prospective drug targets. Typically these teams had five to seven members, drawing heavily on the new technologies of data mining and expression profiling analysis. For many projects, about 80% of the work would be *in silico* and 20% *in vitro.*[28] Biogen might sponsor seven ERPs at a time, each costing around two million dollars per year.

After a formal review, prospective targets would achieve a PEP status where the team members would focus on validating; making sure the target was biologically active, through wet lab biology. These PEP teams generally were composed of about ten people with perhaps eight projects running

[28] About four-fifths of the research, molecule studies, manipulation, and comparison would take place within a computer and various databases. One-fifth would be validated by mixing compounds and trying out lab bench experiments.

at a given time. Each project cost around four million dollars per year. Currently about 10% of this work was *in silico* and 90% *in vitro*.

If a project was successfully validated, it was designated a CIP, or drug candidate, and the team members would again change to people focused on developing and, if the compound was a protein developed in a lab animal, "humanizing" the molecule. This stage took more time than the previous stages. Typically, a CIP team would have 12-15 people and about six projects would simultaneously.[29] In total, CIP teams could include up to seventy-five people and cost close to thirty million per year.[30]

R&D's overall evaluation was measured by the amount of pre-clinical targets that were validated and handed off to product development for clinical trials. This created some tension between the various teams. Differing computer skills and aptitude meant various ERP and PEP teams progressed at different rates as they attempted to make use of the onslaught of data. Steve Perrin, head of the expression-profiling lab, believed: "we flooded [the discovery] pipeline. Some groups managed the information effectively. They usually had one or two key scientists that sat within the disease group who knew what to do with the data once it arrived on their doorstep. Other disease projects were not even close to being prepared…and they've been very slow to push the project forward."

Perrin also felt: "Unfortunately, there is a big dichotomy between the qualifications of the scientists who are willing to embrace genomics and not. The ones who embrace it quickly are the ones who have a lot of interdisciplinary skills. They are good with computers, they are not afraid of technology, and they have a good biological background. Unfortunately some people who are outstanding biologists might not be very computer savvy so they'll want to come in and do a big profiling experiment and you give them the data and they freak out, they panic, they run, and they hide. Scientists that are very good with computers; they dive right in—they ask interesting questions—they know how to deal with the data. They are not afraid to learn things they don't quite understand and they are off and running. The biggest roadblock to my group's success is helping along the people behind the curve."

Biology Bites Back . . .

By its nature, biology, and the need to test drugs *in vivo*, remains a painstaking process.[31] Even after finding a promising target, determining it is biologically active and relatively non-toxic, it takes hundreds of thousands of hours of lab work with cells, animals, and, eventually, increasing number of human subjects to validate a drug and ask for permission to market it.[32] According to John McCoy, Biogen's Vice President Discovery Biology, the real change wrought by high throughput, data

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[29] Time and people estimates come from John McCoy, Vice President Discovery Biology.

[30] Cost figures include 50% added for overhead.

[31] And even when you find a better procedure or molecule, a better method does not necessarily lead to rapid adoption. (Amy C. Edmondson; Richard Bohmer; Gary P. Pisano, "Speeding Up Team Learning," *Harvard Business Review* (October 2001). Furthermore, many scientists are very conservative and secretive because if there is anything a scientist hates it is to be shown to be wrong in public. The community ethos was built on credibility and accuracy; in the words of Victor Koteliansky, Director of Biological Research, "every day is championship day in science. You compete every day. You cannot put out bad data. This is not like politics or finance… two mistakes and no one will speak to you." Furthermore, within the competitive and secretive world of pre-publication science, it was sometimes hard to get researchers to openly share their findings and hypotheses, even within the same company.

[32] Robert Bazell provides a good description of this process in HER-2. Robert Bazell and Amy Bernstein, *HER-2: The Making of a Revolutionary Treatment for Breast Cancer* (Diane Publishing Co., 1998).

intensive processes was to alter the discovery phase. By introducing upfront profiling, scientists in weeks could identify desirable "up- or down-regulated" genes that previously could have taken a lifetime to find.[33]

While there was value to be gained from applying genomics across the value chain, McCoy noted that the research process downstream from initial discovery was not so amenable to high throughput approaches. "Perrin's group generates more data in one afternoon than all the data Biogen had previously generated... the question is how do we turn this into knowledge."

The overall plan was that by being more comprehensive in the initial target identification that there would be higher success rates downstream. But not everyone was happy with the rapid expansion of *in silico* biology. Rich Cate, Biogen's Director, Gene Discovery, felt that "sometimes there is too much hype associated with identifying targets using transcript profiling. They assume that somehow just knowing where a gene is expressed—the value of that information is distorted to the extent that people think you can somehow get function out of it. All you know is where the gene is expressed. To the extent it is a novel protein, you still don't know what it is doing."

Many core founders of Biogen's labs thought that new data sets might be useful in certain areas, but it would be very hard to speed up the actual biological components of drug research. John McCoy put it "Ultimately your research problem will resolve down to a handful of genes, your best candidates, and then it is back to good old-fashioned bench biology."

Having masses of data implied new risks. And not all biologists were pleased with the masses of new data available; to some it represented an unwelcome distraction and risk. Scientist Matvey Lukashev thought, "you cast a bigger net and therefore your chances of picking something up increase. It speeds up the process occasionally. But it sometimes creates a mess if the experiment isn't quite designed right. . . . Every single experiment generates . . . such an incredible amount of numbers and it is so easy to get false leads, and so many of them, that you can spend your life chasing them."

As biology labs faced an ever-larger number of targets to be validated, Biogen began to face a scarcity of researchers skilled in wet biology. Director of Biological Research, Victor Koteliansky argued, "unfortunately you need to go and make wet biology and you need to go on the bench. There is no virtual discovery. . . . Discovery is in wet science or functional stuff." This meant that new discoveries were forced through a big screen. As Steve Perrin, Senior Scientist, explained, "you start off with every gene in the genome, you ask a biological question and it gets honed down to a subset, you do a transcription profiling experiments and you've gone from 50,000 genes to 3,000 genes that might be biologically relevant based on the first experiment. You annotate those and now you are only interested in a subset of 300-400, the next step would probably be cloning those, but you can't clone them all so you prioritize 50, but the antibody guy says I can only make 5 antibodies—finally until you get to the product development guys who say then can only handle four projects per year."

And every time one of these projects began, it started to consume ever-larger amounts of cash (**Exhibits 9** and **10**).

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[33] Genes turn on or off at various points within the cells of particular tissues. You can measure which genes are turned on (up-regulated) and causing a lot of biological activity in a particular tissue. Sometimes essential genes are turned off and fail to attack a disease (down-regulated). By looking at the pattern of gene expression, scientists can sometimes tell whether diseased tissues that exhibit the same symptoms and look the same under a microscope represent different diseases. Golub, et al., "Molecular Classification of Cancer: Class Discovery and Class Prediction by Gene Expression Monitoring," *Science*, vol. 286, 15 October 1999.

The Eos Project

One way to look at the impact of genomics on Biogen in more detail is to look at its breast cancer research operation. During 2000, in an effort to develop drugs to fight breast cancer, Biogen began a partnership with Eos Biotechnology. To find appropriate antibody and protein therapeutic targets, the companies compared millions of data points from diseased and normal breast tissue. Potential targets were then culled using sophisticated statistical tools.

Steve Fawell, Biogen's Associate Director, Oncology, noted that traditionally target genes would crop up in ones or twos. Three years ago Biogen's oncology program had been working on two validated targets. By the end of 2001 it had 25 validated targets, had another 20 queued up for validation, and over 400 more that required initial evaluation. Hundreds more potential targets were piling up every month.

Fawell believed that he could accelerate Phase I slightly, but then drug development became business as usual; "understanding the pre-clinical models for cancer drug development proved to be not as predictive as one would like…if you apply our usual resourcing level, and timelines, and the degree of data we would normally collect prior to going to the clinic, you simply wouldn't be able to get through that list of targets with any speed unless you invested hugely more resources than we currently have."

Evaluating a much larger target list implied hard choices in balancing risk versus speed. In an effort to keep up with exploding opportunities, the oncology group began attempting to collapse steps in the Phase I and Phase II trials. The shift in scope of Stage I clinical trials had significant implications for product development downstream. Typically, process development started considering drug candidates before they completed Phase I so as to ensure quality material was available in a timely way for a Phase II trial. Setting up these manufacturing processes is complex and expensive. This used to be justified because drug candidates were exhaustively studied before entering clinical trials. Now, with many more, less well-understood candidates entering Phase 1, it was unclear when to begin manufacturing. There was also a question as to how to make small amounts of high quality materials for an ever-growing number of targets.

Part of Biogen began testing efficacy in Phase I rather than Phase II. Because Biogen began testing drugs before stringent data verification packets were in place, the company might someday face what could become a very expensive dilemma; the Food and Drug Administration (FDA), which approves all drug sales, makes it harder and harder for a company to change protocols the farther it progresses in clinical trials.

Nevertheless, many Biogen employees were very optimistic. Even though oncology was not within the company's original area of expertise, it was an attractive market because the company could test new drugs and get them to market reasonably fast. FDA approval times are different if the disease is deadly and there are few options.[34] Furthermore, oncology research was compatible with Biogen's new investments in *in silico* biology; the biological mechanisms underlying other specialties, such as neurology, were far less understood and would therefore be harder to industrialize.

[34] Various biotech and pharmaceutical companies are pursuing similar strategies focused on oncology. In 2000, there were 396 cancer drugs in Phase II and 144 cancer drugs in Phase III. Mark P. Mathieu (editor), *Parexel's Pharmaceutical R&D Statistical Sourcebook 2001*, p. 51.

Biogen's Future . . .

Jim Mullen knew his company was changing rapidly. Biogen had incorporated a lot of new tools in a short period of time. Five years ago, a large pharmaceutical company would generate around 100 Gigabytes of data per year. Biogen was now doing this every three months.[35] He now had access to enormous data sets on gene expression, toxicology, effectiveness and surrogate markers for clinical trials. New *in silico* tools, as well as novel technologies such as protein sequencing technologies (proteomics), promised to increase incoming data by orders of magnitude yet again.

But as more drug candidates entered the front end of the drug development pipeline, enthusiasm for genomics was tempered by the bottleneck created at slow biology stages. Those at the front end of Biogen's discovery chain felt that they were producing an enormous wealth of knowledge and were frustrated by the laborious process followed in clinical trials. Those at the back end of the discovery cycle felt that bioinformaticians did not understand what they did, nor did they understand the subtlety and complexity of biological organisms.

But if Biogen were to remain competitive, it would have to continue making large investments now in unproven targets. Already during 1999-2000, the company had spent $81 million expanding its Cambridge headquarters and laboratories. With the significant increase in targets to validate, work within molecular biology labs began to change quickly; rather than nurse one or two targets through all phases of the validation process, scientists and their technicians were specializing in certain "packets" or discreet steps. (See **Exhibit 11**.) Results were measured on how many targets they could process.

Through 2002 the company was planning to add 120,000 sq. ft. of new lab space. Plans for further expansions were moving ahead rapidly. Architects and facilities managers kept a frantic pace. Instead of a dry pipeline, Biogen now faced an "embarrassment of riches," uncovered during the last R&D product review. A much larger number of drug candidates might soon enter pre-clinical and clinical evaluation. Emphasis began to shift from identifying targets towards to how to utilize genomics tools to improve the success rate of drug candidates.

Mullen's publicly stated goal was to double revenues within five years. Yet as Biogen attempted to move from a few products to masses of targets, even this jump in revenues would be a drop in the bucket compared with the pharmaceutical behemoths. (See **Exhibit 12**.) As a tidal wave of data and of new opportunities washed over Biogen, how might the CEO have to restructure various areas including manufacturing, finance, marketing, and drug development? Would doubling revenues provide sufficient scale for Biogen to prosper in this new biotech environment? Would it make sense to adopt a niche strategy or grow into the various opportunities?[36]

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[35] Estimate by Steve Perrin. A large pharma company would now generate at least five times more data than Biogen.

[36] On a larger scale Mullen also had to consider whether the changes occurring within Biogen were occurring elsewhere, how might this alter the overall drug market? Costs? Regulation? Relative competitiveness?

Exhibit 1a Biogen, Inc. and Subsidiaries Consolidated Financial Statements

Profit and Loss Statement

(in US $ thousands, except per share amounts)

	2001	2000	1999	1998	1997	1996
Revenues						
Product	$ 971,594	$ 761,079	$ 620,636	$ 394,863	$ 239,988	$ 78,202
Royalties	$ 71,766	$ 165,373	$ 173,799	$ 162,724	$ 171,921	$ 181,502
Total Revenues	$ 1,043,360	$ 926,452	$ 794,435	$ 557,587	$ 411,909	$ 259,704
Cost and Expenses						
Cost of Revenues	$ 136,510	$ 125,198	$ 111,005	$ 74,509	$ 50,188	$ 28,525
Research and development	$ 314,556	$ 302,840	$ 221,153	$ 177,228	$ 145,501	$ 132,384
Selling, general and administrative	$ 232,096	$ 170,058	$ 146,026	$ 115,211	$ 90,098	$ 73,632
Total Cost and Expenses	$ 683,162	$ 598,096	$ 478,184	$ 366,948	$ 285,787	$ 234,541
Income from Operations	$ 360,198	$ 328,356	$ 316,251	$ 190,639	$ (45,799)	$ (156,336)
Other income (expense) net	$ 29,299	$ 158,749	$ 12,765	$ 19,554	$ 194,767	$ 197,168
Income before income tax	$ 389,497	$ 487,105	$ 329,016	$ 210,193	$ 148,968	$ 40,829
Income Taxes	$ 116,814	$ 153,528	$ 108,566	$ 71,496	$ 59,801	$ 299
Net Income	$ 272,683	$ 333,577	$ 220,450	$ 138,697	$ 89,167	$ 40,530
Basic Earnings per share	$ 1.84	$ 2.24	$ 1.47	$ 0.94		
Diluted earnings per share	$ 1.78	$ 2.16	$ 1.40	$ 0.90	$ 0.58	$ 0.28
Shares used in calculating:						
Basic earnings per share	148,355	148,743	149,788	147,537		
Diluted earnings per share	152,916	154,602	157,788	154,270	152,999	146,442

Source: Biogen, Inc. 2000 Annual Report; SEC filings.

Exhibit 1b Biogen, Inc. and Subsidiaries Consolidated Financial Statements

Condensed Consolidated Balance Sheets
(in US $ thousands)

	2001	2000	1999
Assets			
Current Assets			
Cash and cash equivalents)		$ 48,737	$ 56,920
Cash and marketable securities	$ 798,107	$ 633,675	$ 597,619
Accounts receivable, net	$ 177,582	$ 143,178	$ 137,363
Other current assets	$ 122,038	$ 102,681	$ 118,324
Total current assets	$ 1,097,727	$ 928,271	$ 910,226
Property and equipment, net	$ 555,998	$ 400,429	$ 239,777
Other assets	$ 67,321	$ 103,156	$ 127,970
Total Assets	$ 1,721,046	$ 1,431,856	$ 1,277,973
Liabilities and Shareholders' Equity			
Current Liabilities	$ 294,942	$ 221,021	$ 190,270
Long term debt & liabilities	$ 77,272	$ 104,433	$ 108,173
Shareholders' equity	$ 1,348,832	$ 1,106,402	$ 979,530
Total Liabilities and Shareholders' Equity	$ 1,721,046	$ 1,431,856	$ 1,277,973

Sources: Biogen, Inc. 2000 Annual Report

"Biogen Delivers on Operating Earnings Guidance of $1.90 per Share After One-Time Charges," *PR Newswire*, January 24, 2002.

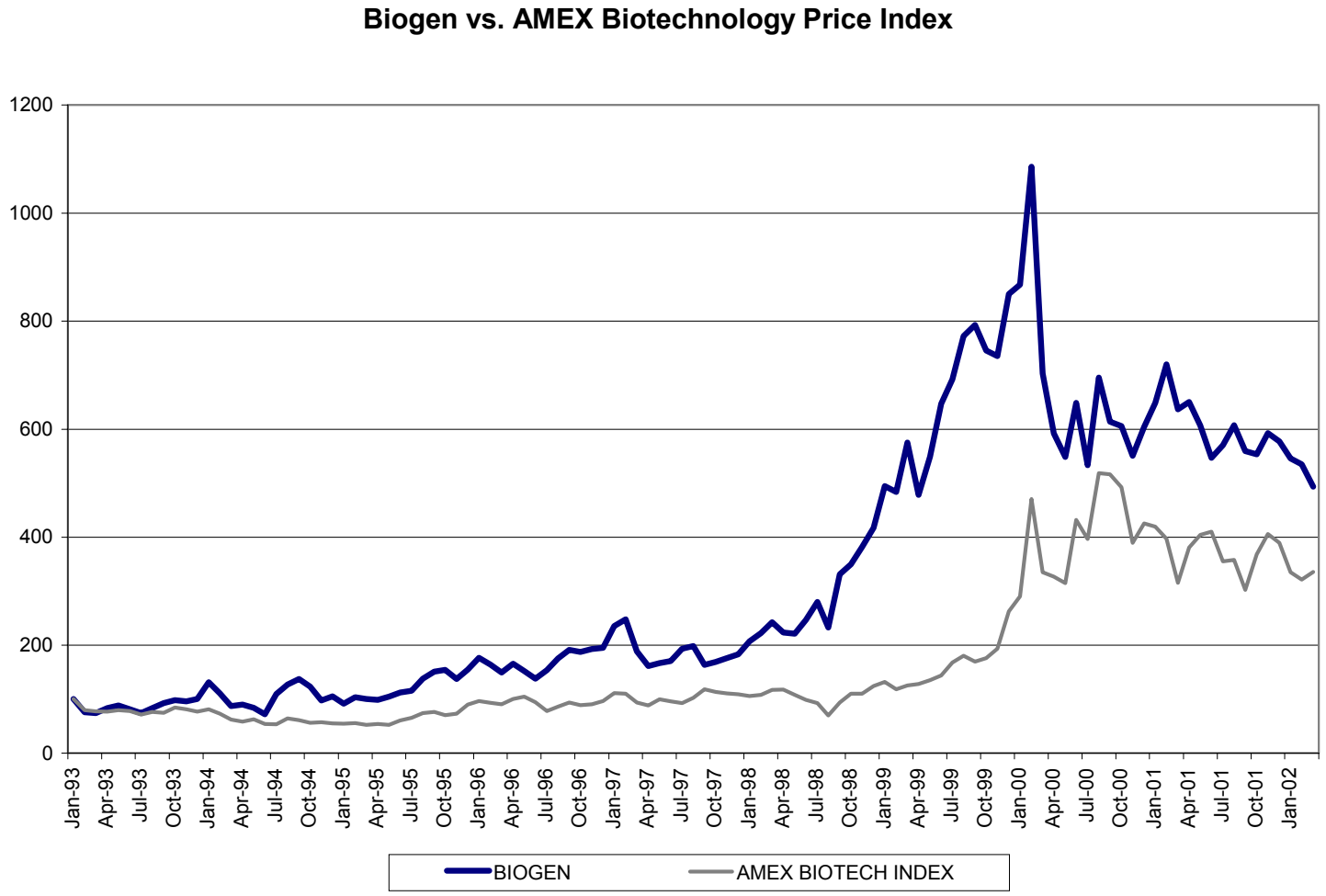
Exhibit 1c Biogen, Inc. and Subsidiaries Consolidated Financial Statements

Sources and Uses
(in US $ thousands)

For the years ended December 31,	2000	1999	1998
Cash Flow from Operations			
Net Income	$ 333,577	$ 220,450	$ 138,697
Adjustments to reconcile net income to net cash provided from operating activities			
Depreciation and amortization	$ 38,824	$ 31,099	$ 24,590
Other	$ (569)	$ 5,162	$ (888)
Deferred income taxes	$ 25,203	$ (23,981)	$ 7,486
Gain on sale of non-current marketable securities	$ (101,129)	-------	-------
Tax benefit of stock options	$ 81,023	$ 91,295	$ 19,595
Write-down of non-current marketable securities	-------	$ 15,287	-------
Changes in:			
Accounts receivable	$ (5,815)	$ (36,082)	$ (14,479)
Other current and other assets	$ (35,329)	$ (41,372)	$ (25,638)
Accounts payable, accrued expenses and other current and long-term liabilities	$ 30,154	$ 101,725	$ 38,077
Net cash flows from operating activities	$ 365,939	$ 363,583	$ 187,440
Cash Flow from Investing Activities			
Purchases of marketable securities	$ (627,168)	$ (1,120,218)	$ (574,021)
Proceeds from sales and maturities of marketable securities	$ 606,087	$ 1,006,465	$ 453,952
Proceeds from sales of non-current marketable securities	$ 120,199	-------	-------
Investment in collaborative partners	$ (5,000)	$ (10,000)	$ (5,000)
Acquisitions of property and equipment	$ (194,402)	$ (82,528)	$ (29,049)
Additions to patents			
Net cash flows from investing activities	$ (104,997)	$ (210,080)	$ (158,680)
Cash Flow from Financing Activities			
Repayments on note payable	-------	-------	$ (24,817)
Repayments on long-term debt	$ (4,888)	$ (4,887)	$ (4,886)
Purchases of treasury stock	$ (300,192)	$ (197,717)	$ (65,550)
Proceeds from put warrants	-------	$ 22,086	-------
Issuance of common stock and option exercises	$ 35,955	$ 58,490	$ 21,580
Net cash flows from financing activities	$ (269,125)	$ (122,028)	$ (73,673)
Net increase (decrease) in cash and cash equivalents	$ (8,183)	$ 31,475	$ (44,913)
Cash and cash equivalents, beginning of the year	$ 56,920	$ 25,445	$ 70,358
Cash and cash equivalents, end of the year	$ 48,737	$ 56,920	$ 25,445
Supplemental Cash Flow Data			
Cash paid during the year for:			
Interest	$ 4,314	$ 4,598	$ 5,909
Income taxes	$ 42,683	$ 4,787	$ 35,828

Source: Biogen, Inc. 2000 Annual Report.

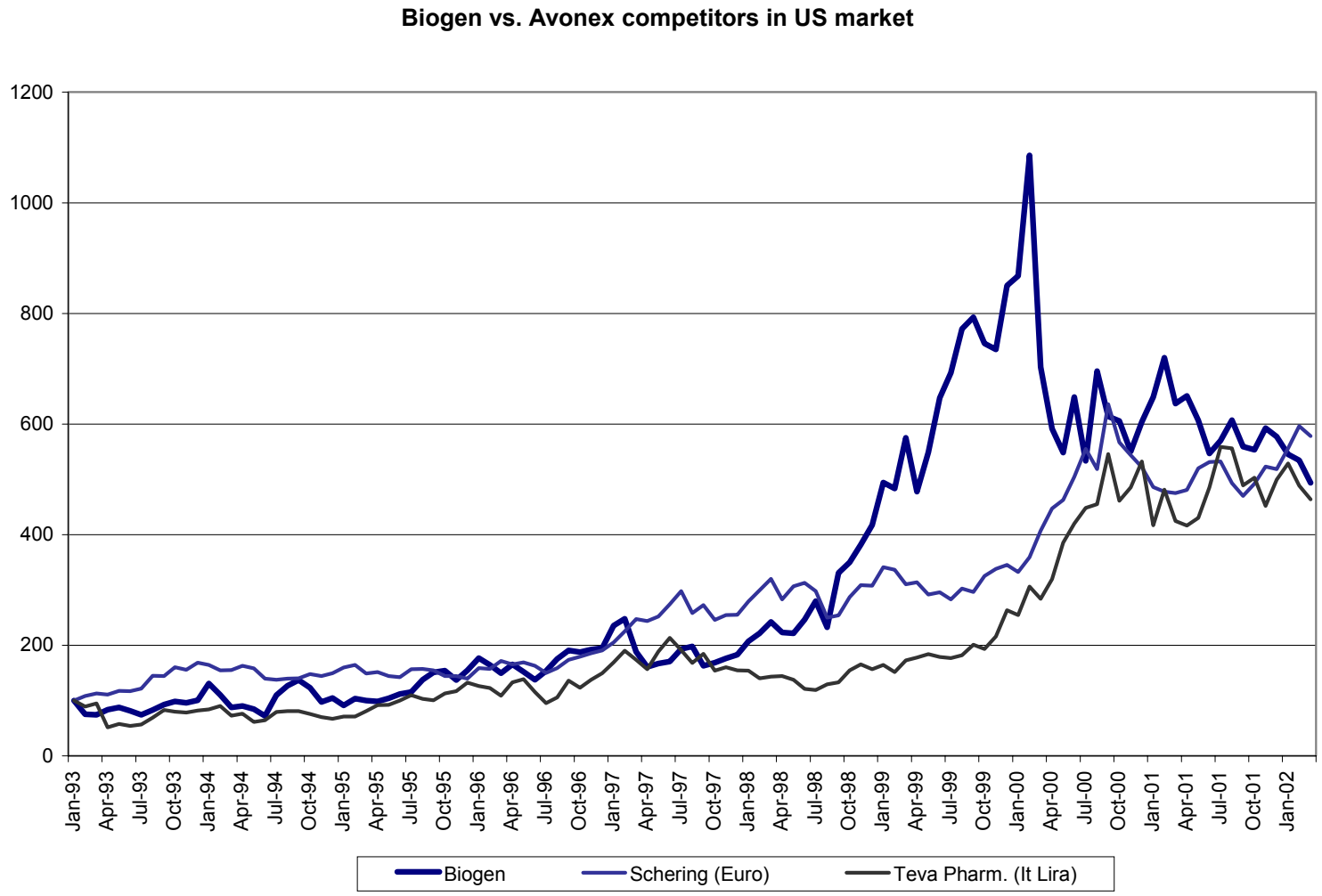
Exhibit 2a Biogen's Stock Performance Compared with Biotechnology Index and Direct Competitors



Source: Datastream.

Note: Prices have been indexed to 100.

Exhibit 2b Biogen's Stock Performance Compared with Biotechnology Index and Direct Competitors



Source: Datastream

Note: Prices have been indexed to 100.

Exhibit 3 Top Worldwide Biotech and Pharmaceutical Acquisitions 2000-to-Date

Date Effective	Acquiror Name	Target Name	Target Business Description	Value of Transaction ($mil)
06/19/00	Pfizer Inc	Warner-Lambert Co	Health care,consumer products	$ 89,168
12/27/00	Glaxo Wellcome PLC	SmithKline Beecham PLC	Manufacture pharmaceuticals	$ 75,961
03/31/00	Monsanto Co	Pharmacia & Upjohn Inc	Mnfr pharmaceutical prods	$ 26,486
06/22/01	Johnson & Johnson	ALZA Corp	Manufacture pharmaceuticals	$ 11,070
10/02/01	Bristol-Myers Squibb Co	DuPont Pharmaceuticals Co	Mnfr,whl pharmaceutical prods	$ 7,800
03/02/01	Abbott Laboratories	Knoll AG(BASF AG)	Manufacture pharmaceuticals	$ 6,900
08/06/01	Shareholders	Zimmer Holdings Inc	Mnfr,whl orthopedic implants	$ 5,801
10/17/00	Tyco International Ltd	Mallinckrodt Inc	Mnfr diagnostic products	$ 4,393
04/25/00	Linde AG	AGA AB	Mnfr industrial,medical gases	$ 4,083
05/11/01	Shire Pharmaceuticals Group	BioChem Pharma Inc	Mnfr pharmaceuticals	$ 3,748
08/31/00	King Pharmaceuticals Inc	Jones Pharmaceutical Inc	Mnfr drug products, vitamins	$ 3,523
08/28/01	Medtronic Inc	MiniMed Inc	Mnfr,whl microinfusion systems	$ 3,304
03/29/00	Cia di Partecipazioni Assicura	Montedison(Cie de Partecipazi)	Mnfr chemicals,pharmaceuticals	$ 3,115
02/12/02	Millennium Pharmaceuticals Inc	COR Therapeutics Inc	Mnfr pharmaceuticals	$ 2,417
07/10/00	Koninklijke Numico NV	Rexall Sundown Inc	Mnfr,whl vitamins	$ 1,768
11/10/00	Elan Corp PLC	Dura Pharmaceuticals Inc	Mnfr pharmaceuticals	$ 1,708
08/01/01	Koninklijke Philips Electronic	Agilent Tech-Healthcare Solut	Mnfr medical monitoring equip	$ 1,700
01/15/02	MedImmune Inc	Aviron	Mnfr biological products	$ 1,665

Exhibit 3 (continued)

Date Effective	Acquiror Name	Target Name	Target Business Description	Value of Transaction ($mil)
03/16/00	Adecco SA	Olsten Corp	Pvd temporary staffing svcs	$ 1,475
09/14/00	Invitrogen Corp	Dexter Corp	Mnfr adhesives,coatings	$ 1,468
04/27/01	Triad Hospitals Inc	Quorum Health Group Inc	Own,op acute care hospitals	$ 1,400
01/31/02	WellPoint Health Networks Inc	RightCHOICE Managed Care Inc	Own,operate HMOs,PPOs	$ 1,347
11/21/01	Johnson & Johnson	Inverness Medical-Diabetes	Mnfr diabetes-treatment prod	$ 1,300
01/16/01	SmithKline Beecham PLC	Block Drug Co	Mnfr dental prod,pharmaceutica	$ 1,235
09/28/01	Mayne Nickless Ltd	FH Faulding & Co Ltd	Mnfr,whl drugs,toiletries	$ 1,218
11/10/00	GN Store Nord A/S	Photonetics SA	Mnfr photonic instruments	$ 1,190
02/28/01	Sasol Ltd	Condea Chemie GmbH(RWE)	Mnfr chemicals and elastomers	$ 1,142
03/11/02	L-3 Communications Holdings	Raytheon Co-Aircraft Intgrtion	Mnfr military aircraft	$ 1,130
10/01/01	Welfide Corp	Mitsubishi-Tokyo Pharm	Mnfr synthetic organic fibers	$ 1,129
10/19/01	Koninklijke Philips Electronic	Marconi plc-Medical Operations	Mnfr diagnostic imaging equip	$ 1,100
12/14/00	Genzyme Corp	GelTex Pharmaceuticals Inc	Mnfr pharmaceuticals	$ 1,052
10/03/00	Advance Paradigm Inc	PCS Health Systems(Rite Aid)	Pvd drug benefit mgmt svcs	$ 1,022
09/01/00	Alcon Laboratories Inc(Nestle)	Summit Autonomous Inc	Mnfr,whl opthalmic laser sys	$ 929
08/28/00	Watson Pharmaceuticals Inc	Schein Pharmaceutical Inc	Manfacture pharmaceuticals	$ 916
01/24/00	Celltech Chiroscience PLC	Medeva PLC	Pvd medical research services	$ 914
12/22/00	Corixa Corp	Coulter Pharmaceuticals Inc	Mnfr cancer pharmaceuticals	$ 854
03/31/00	Shareholders	Baxter-Cardiovascular Bus	Mnfr cardiovascular prods	$ 798
10/03/00	Ciba Vision Corp(Ciba-Geigy)	Wesley Jessen(Bain Capital)	Mnfr ophthalmic goods, equip	$ 759
09/28/01	Investor Group	Carter-Wallace Inc-Consumer	Mnfr consumer products	$ 739
09/22/00	Chiron Corp	PathoGenesis Corp	Mnfr pharmaceuticals	$ 700

Source: Adapted from SDC Mergers and Acquisitions.

Exhibit 4 Multiple Sclerosis Population

Patient Population

Region	Estimated Population with MS
U.S.	350,000
Europe	350,000
Rest of World (ROW)	1,300,000

Source: Adapted from Morgan Stanley Research, Biogen Report, "MS Franchise Provides Near-Term Opportunity," September 18, 2001.

Biogen's AVONEX is approved for Relapsing Remitting Multiple Sclerosis. There are several other forms of the disease.

Categories of Multiple Sclerosis	% of US Disease Population (estimated 350K people)
Relapsing Remitting MS	45.0
Secondary Progressive MS	25.0
Primary Progressive MS	10.0
Relapsing Progressive MS	10.0
Monosymptomatic MS	10.0

Source: Adapted from Morgan Stanley Research, Biogen Report, "MS Franchise Provides Near-Term Opportunity," September 18, 2001.

Note: Drugs must be approved by the FDA for each category of multiple sclerosis.

Relapsing Remitting MS is characterized by "attacks " of the disease on nerve myelin coverings followed by periods of remission. *Secondary Progressive MS* is experienced similar to RRMS, although the nerves sustain more damage and this form of the disease is more difficult to treat than RRMS. *Primary Progressive MS* is characterized by a gradual decline in nerve function without acute attacks, and does not respond well to existing treatments. *Monosymptomatic MS* is characterized by a single attack by the disease. Biogen's CHAMPS study demonstrated efficacy in preventing recurrence of attacks in Monosymptomatic MS patients.

Exhibit 5 Multiple Sclerosis Market

Estimated Market Size: $2 billion worldwide in 2001, rising to $4 billion by 2005.

Source: Merrill Lynch Analyst Report.

Market Share

United States	
Biogen	53%
Teva	28%
Schering	19%
Total	100%

Europe	
Biogen	34%
Teva	5%
Schering	34%
Serono	27%
Total	100%

Source: Adapted from IMS Health via Morgan Stanley Research; Morgan Stanley Research Biogen Report, September 18, 2001.

"MS Franchise Provides Near-Term Opportunity," Caroline L. Copithorne, et al.

N.B. AVONEX was developed for the U.S. market under the Orphan Drug program. The underlying patent and the orphan drug status both expire in 2003, at which time Serono was to be allowed to enter the U.S. market with their version of a similar drug, Rebif. In early March 2002, the FDA determined that Serono would be permitted to sell Rebif in the U.S. Market affective immediately.

Company	Sales	R&D Exp.	Market Value
For Year Ending December 31, 2000			
(US $ Millions)			
Schering AB	$ 4,316	$ 1,267	$ 11,274
Serono S.A.	$ 1,147	$ 263	$ 21,700
Teva Pharmaceuticals	$ 1,750	$ 105	$ 9,370
Biogen	$ 927	$ 303	$ 8,878

Source: Hoover's Online; SEC filings.

Exhibit 6 Two Views on the Costs and Uncertainties of Drug Development

	Probabilities of Success by Phase				
Stage	**Avg. Duration (years)**	**% success**	**% cumulative success**	**Avg. $ per stage (US $ mil)**	**% R&D exp per stage**
Target Identification	1			165.0	19%
Target Validation	2	5	4.5	205.0	23%
Screening	0.4	13	5.8	40.0	5%
Optimization	2.7	53	3.0	120.0	14%
Pre Clinical	1.6	42	1.3	90.0	10%
Clinical	7	23	0.3	260.0	30%
Total	14.7			880.0	100%

Source: Adapted from "A Revolution in R&D: How Genomics and Genetics Are Transforming the Biopharmaceutical Industry," BCG Report November 2001. % success per stage derived from bar charts in Exhibit 5, p. 20. Duration and Cost per Stage from Exhibit 2, p. 12.

Costs include cost of failed projects.

	Probabilities of Success by Phase				
Stage	**Avg. Duration (years)**	**% success**	**% cumulative success**	**Avg. $ per stage (US $ mil)**	**% R&D exp per stage**
Target Validation	)	30-35	30	)	
Hit Generation	) 2.5	90	27	) 60.4	4%
Lead optimization	))	90	24	))	
Biological validation	)) 3	75	18	)) 226.5	15%
Pre Clinical	1	50	9	151.0	10%
Phase 1	1.5	70	6	226.5	15%
Phase 2	2	50	3	332.2	22%
Phase 3	2.5	70	2	468.1	31%
FDA filing	1.5	90	2	45.3	3%
Total	14			1510.0	100%

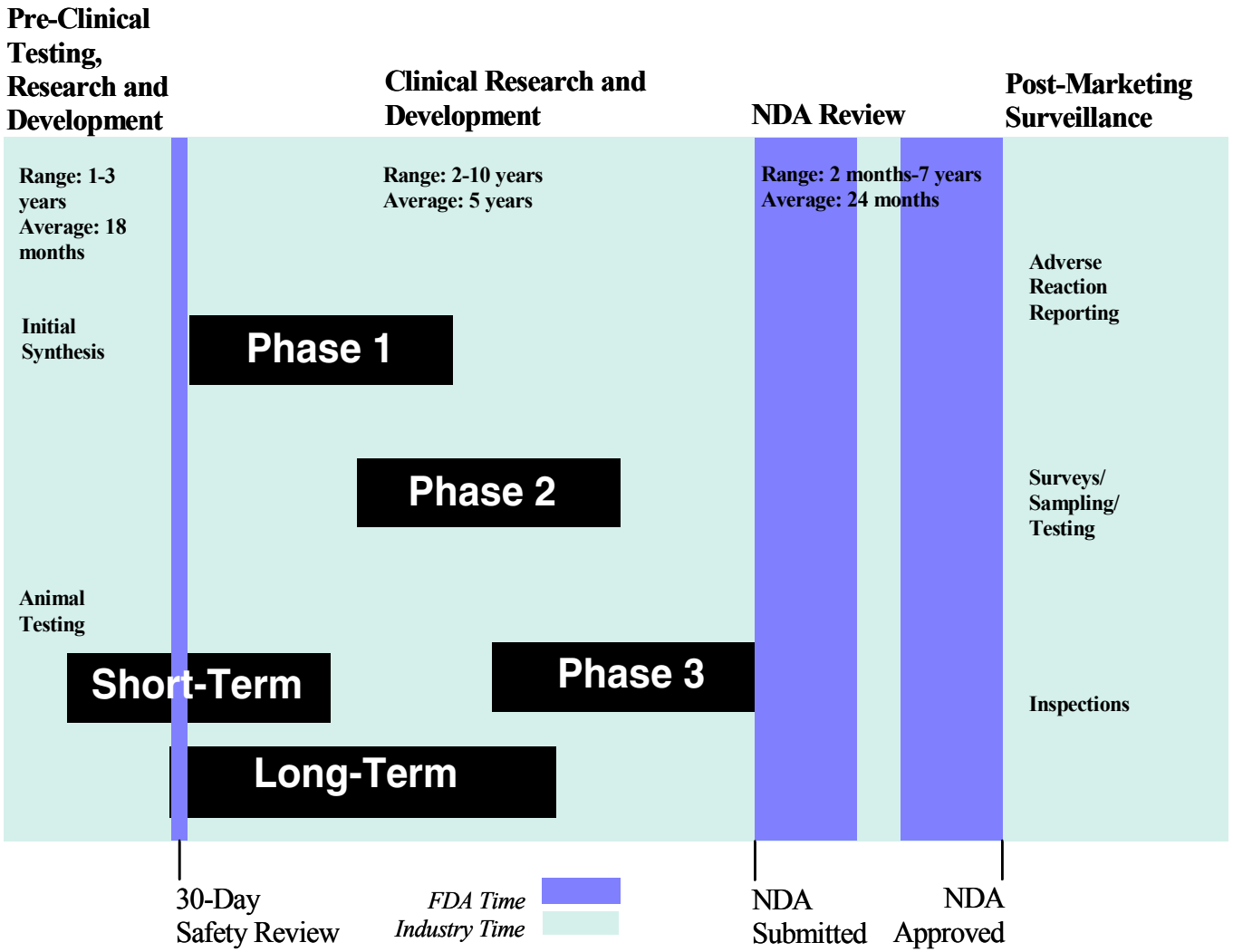
Sources: Adapted from "The Fruits of Genomics," Lehman Brothers Study, Slide 3, p. 22. "The Fruits of Genomics II Analyst Forum," January 2001, Lehman Brothers Study. Note: $ per stage amounts derived using percents from Figure 22, p. 46, and total % per drug from Figure 24, p. 48.

N.B. Tufts Center for the Study of Drug Development announced that the average cost to develop a new drug is $802 million. This figure included the cost of project failures, the impact of long development times on investment costs, and was based on surveys of 10 drug companies.

Source: Tufts Center for the Study of Drug Development press release, November 30, 2001.

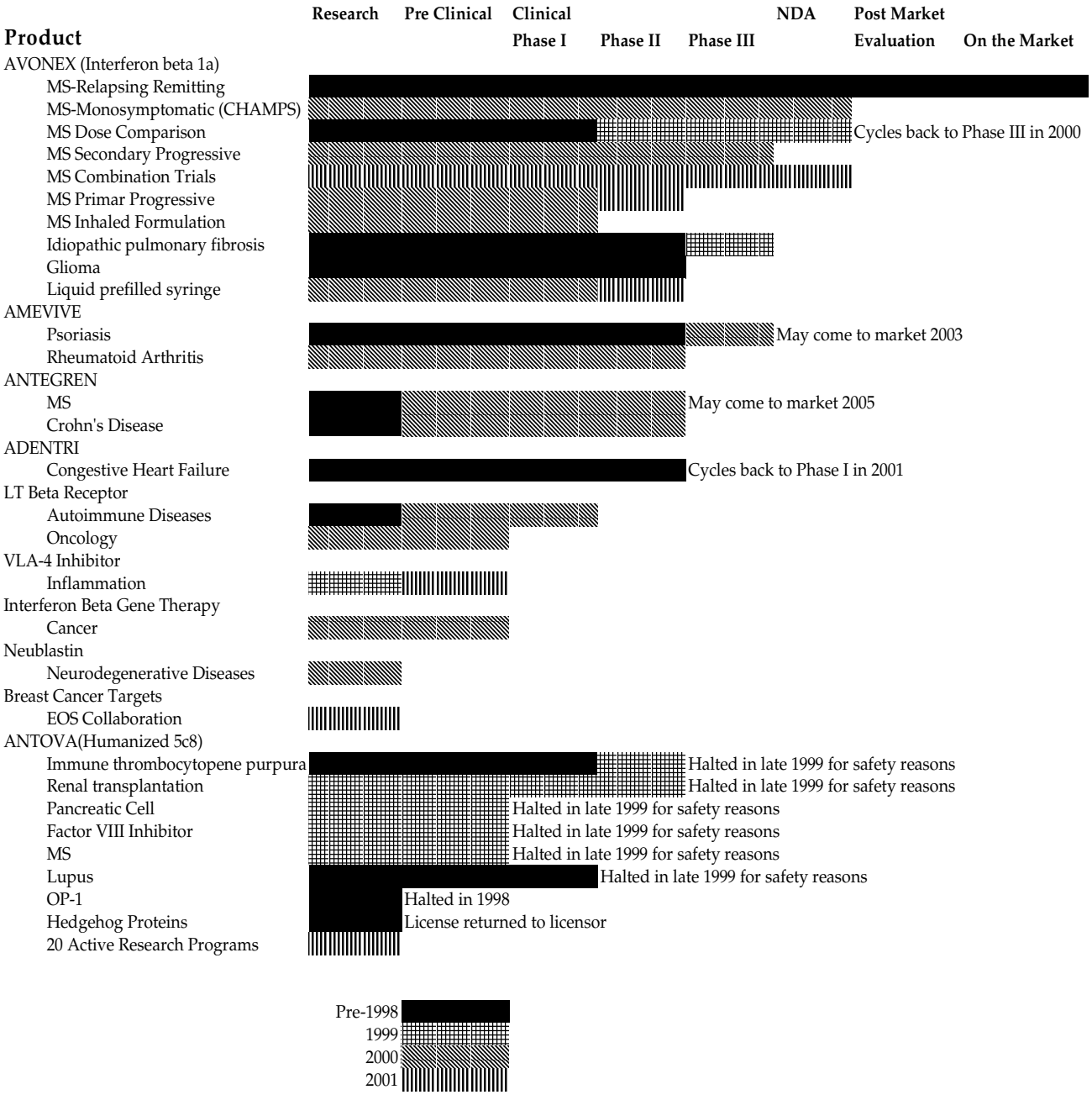
Exhibit 7

New Drug Development Timeline



Source: http://www.fda.gov/fdac/graphics/newdrugspecial/drugchart.pdf.

Exhibit 8 Biogen, Inc. Product Pipeline Evolution



Source: Compiled from Biogen, Inc. Annual Reports.

Exhibit 9 Breakdown of Biogen's R&D Expenditures

Estimated Distribution of R&D Spending by Development Phase

Development Stage	% R&D Spending*	Biogen 2001 (USD Mil)	# projects beg. 2001	$/project (USD Mil)
Basic Research	4%	$ 12.58	NA	
Discovery	15%	$ 47.18	NA	
Preclinical Development	10%	$ 31.46	2	$ 15.73
Clinical Development				
Phase 1	15%	$ 47.18	5	$ 9.44
Phase 2	22%	$ 69.20	3	$ 23.07
Phase 3	31%	$ 97.51	3	$ 32.50
FDA filing through approval	3%	$ 9.44	1	$ 9.44
Total	100%	$ 314.6		

Source: Created by casewriter based on data from "The Fruits of Genomics II," Lehman Brothers, January 2001. Biogen, Inc. Annual Report and company product pipeline data at www.Biogen.com, January 2001.

*Breakdown of R&D spending per "The Fruits of Genomics II," p. 46. Chart cites McKinsey & Co., Lehman Brothers, PhRMA and FDA as sources.

Biogen Expense by stage based on Lehman percentages. However, in company interviews, Biogen estimated it spends 30% of its R&D budget on research prior to the preclinical stage.

Biogen 2001 R&D expenditure preliminary figure released January 2002.

Exhibit 10 Biogen's Cost of Drug Development

Cost of R&D to bring 2000 pipeline to market

Projects per Phase per Year
(Full Year Equivalents)

Stage	Duration (years)	Prob of success	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Pre clinic	1.5	0.8	1.00	0.50								
Phase 1	1.5	0.7	4.00	2.40	0.80	0.00						
Phase 2	2	0.5	2.00	3.40	2.80	1.96	0.56	0.00				
Phase 3	2.5	0.7	8.00	8.00	5.00	1.70	1.90	1.68	0.28	0.14		
FDA filing	1.5	0.9	3.00	1.50	2.80	5.60	0.35		0.98	0.20		
Market				1.35			5.04	0.63		0.88	0.18	
Total	9											

Methodology: These figures were not provided by the company but reflect the casewriter's estimates based on industry information.
Progress of drug candidates noted in Biogen 2000 Annual Report were tracked forward and updated to end of 2001.
Projections utilizing industry probabilities and durations were then applied to this portfolio.
Duration: Durations for each phase from "The Fruits of Genomics II Analyst Forum", January 30, 2001, Fig. 22, p. 46.
Duration does not include discovery stage activities.

Probability of success derived from the following sources:
Pre clinical: Company interviews
Clinical by Phase & FDA : "The Fruits of Genomics", Lehman Brothers, January 30, 2001, p. 22.

N.B. Five of the Phase 3 projects in 2002 are Avonex product extensions.

Cost per project per stage per year adjusted for inflation

Stage	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Pre clinic	$ 15,730	$ 16,517	$ 17,342	$ 18,209	$ 19,120	$ 20,076	$ 21,080	$ 22,134	$ 23,240	$ 24,402
Phase 1	$ 9,440	$ 9,912	$ 10,408	$ 10,928	$ 11,474	$ 12,048	$ 12,651	$ 13,283	$ 13,947	$ 14,645
Phase 2	$ 23,070	$ 24,224	$ 25,435	$ 26,706	$ 28,042	$ 29,444	$ 30,916	$ 32,462	$ 34,085	$ 35,789
Phase 3	$ 32,500	$ 34,125	$ 35,831	$ 37,623	$ 39,504	$ 41,479	$ 43,553	$ 45,731	$ 48,017	$ 50,418
NDA	$ 9,440	$ 9,912	$ 10,408	$ 10,928	$ 11,474	$ 12,048	$ 12,651	$ 13,283	$ 13,947	$ 14,645
Market										

Inflation factor 0.05
Per project per stage figures were derived by applying percentages from Exhibit 9 to each stage and dividing by the number of projects.

Exhibit 10 (continued)

Estimated Cost of R&D to bring 2000 pipeline to market
(US$ '000)

Stage	Duration years	Prob of success	2002	2003	2004	2005	2006	2007	2008	2009	2010
Pre clinic	1.5	0.8	$ 15,730	$ 8,258	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Phase 1	1.5	0.7	$ 37,760	$ 23,789	$ 8,326	$ -	$ -	$ -	$ -	$ -	$ -
Phase 2	2	0.4	$ 46,140	$ 82,360	$ 71,217	$ 52,345	$ 15,703	$ -	$ -	$ -	$ -
Phase 3	2.5	0.7	$ 260,000	$ 273,000	$ 179,156	$ 63,959	$ 75,058	$ 69,685	$ 12,195	$ 6,402	$ -
NDA	1.5	0.12	$ 28,320	$ 14,868	$ 29,141	$ 61,197	$ 4,016	$ -	$ 12,397	$ 2,603	$ -
Market			$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Total			$ 387,950	$ 402,275	$ 287,841	$ 177,500	$ 94,777	$ 69,685	$ 24,592	$ 9,006	$ -

Total required to pursue existing pipeline	$ 1,453,626	R&D investment required to support 2000 pipeline through launch
	$ 979,110	R&D investment from launch of Avonex up to 2000
	$ 2,432,736	Total R&D invested in new drugs since AVONEX launched

Source: Casewriter's estimates based on industry information.

Exhibit 11 Discovery and Exploration Process for the EOS Project

1)	Tissue Access	
2)	Running Affymetrix chips	Done by EOS Biogen developed access to tissue; some affymetrix chips run in-house
3)	Expression Mining	This step is a handoff from Affymetrix Lab / Bioinformatics specialists and wet lab scientists
4)	Sequence Mining	An overlapping team of "wet lab" scientists and "in silico" focused Scientists select best targets
5)	Cloning Group	Makes full length CDNA for every target selected
6)	Expression Group	Takes clones and puts into other vectors to support protein production
7)	Protein Purification Group	
8)	Monoclonal Antibody Facility	Inject protein into mice
9)	Pharmacology Group	Xenograft models (human tumors) test for efficacy
10)	Humanize antibody	
11)	Put Humanized Antibody into biology	Verify antibody still effective
12)	If Successful, Candidate Passes to Pre-Clinical Drug Development Stage	

Source: Company interview.

Exhibit 12 Top Pharmaceutical and Biotechnology Companies Ranked by Market Value End 2000 (in US$ millions)

	Sales/ Turnover (Net)	Market Value
PFIZER INC	$ 29,574	$ 290,444
MERCK & CO	$ 40,363	$ 216,049
GLAXOSMITHKLINE PLC	$ 27,413	$ 175,768
JOHNSON & JOHNSON	$ 29,139	$ 146,135
BRISTOL MYERS SQUIBB	$ 18,216	$ 144,440
NOVARTIS AG	$ 21,226	$ 115,214
LILLY (ELI) & CO	$ 10,862	$ 104,747
ASTRAZENECA PLC	$ 18,103	$ 89,034
AMERICAN HOME PRODUCTS CORP	$ 13,263	$ 83,363
SCHERING-PLOUGH	$ 9,815	$ 83,025
PHARMACIA CORP	$ 18,144	$ 79,074
ABBOTT LABORATORIES	$ 13,746	$ 74,881
AMGEN INC	$ 3,629	$ 66,329
SANOFI-SYNTHELABO	$ 5,510	$ 48,757
TAKEDA CHEMICAL INDUSTRIES	$ 8,729	$ 42,932
GENENTECH INC	$ 1,646	$ 42,826
IMMUNEX CORP	$ 862	$ 21,972
TEVA PHARMACEUTICALS	@NA	$ 17,686
ELAN CORP PLC	$ 1,302	$ 15,175
MILLENNIUM PHARMACTCLS INC	$ 196	$ 13,240
ALLERGAN INC	$ 1,626	$ 12,748
YAMANOUCHI PHARMACEUT CO LTD	$ 4,148	$ 12,450
NOVO NORDISK A/ S	$ 2,580	$ 11,597
SCHERING AG	$ 4,151	$ 11,246
SERONO SA	$ 1,147	$ 11,223
FOREST LABORATORIES	$ 1,175	$ 10,462
MEDIMMUNE INC	$ 540	$ 10,079
IDEC PHARMACEUTICALS CORP	$ 155	$ 9,280
SANKYO CO LTD (PHARMACEUTCL)	$ 4,938	$ 9,041
BIOGEN INC	$ 926	$ 8,879
KING PHARMACEUTICALS INC	$ 620	$ 8,830
HUMAN GENOME SCIENCES INC	$ 22	$ 8,677
GENZYME CORP	$ 752	$ 8,588

Source: Adapted by casewriter from Compustat Global Vantage.