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GlaxoSmithKline: Reorganizing Drug Discovery (A)

Tadataka "Tachi" Yamada looked in awe at the snow-covered mountains outside his window. He realized that, while those mountains were currently a source of fun and recreation for his family, they were also a place where thousands of skiers and hikers took significant risks on a daily basis. Now, in February 2000, Yamada was preparing to embark on the riskiest venture of his 25-year career in medicine and pharmaceutical research. Currently the head of research and development (R&D) for pharmaceutical giant SmithKline Beecham, Yamada had been notified three weeks earlier that—as of July 2000—he would become Chairman of R&D for GlaxoSmithKline (GSK), which was to be created by the planned merger of SmithKline Beecham and Glaxo Wellcome. He knew that this vacation might be the last one he would have for quite some time.

Upon appointing Yamada to his new position, GSK's CEO, Jean-Pierre Garnier, encouraged him to think about creative mechanisms for solving the biggest problem facing GSK—the declining productivity of pharmaceutical R&D. Garnier, who was then CEO of SmithKline Beecham, had worked closely with Yamada in the past and was confident that Yamada had a keen sense of the magnitude of the productivity problem, not only for GSK, but across the entire pharmaceutical industry. From Yamada's perspective the large firms that had traditionally dominated the industry were plagued by excessive bureaucracy, poor communication across and within functional areas, and a general lack of what he termed an "entrepreneurial spirit".

In the three weeks since the announcement of the GSK merger, Yamada had already sketched out a dramatic restructuring of drug discovery at GSK. His proposal involved dividing the planned total of roughly 1,900 drug-discovery scientists at GSK into six distinct "centers of excellence in drug discovery" (CEDDs), each focused on one-to-three therapeutic areas. While relying on essentially the same pool of research scientists currently available at Glaxo Wellcome and SmithKline Beecham, Yamada felt that the CEDDs promised to improve research productivity at GSK significantly by simultaneously leveraging the benefits of scale in certain areas and focus in others. He had already received support for his overall restructuring plan from Garnier and the R&D Integration Committee, which was comprised of senior R&D executives from each of the heritage organizations. Now, he needed to finalize the details of this new structure and implement it in time for the planned closing of the merger. He had only five months.

Professor Robert S. Huckman and Research Associate Eli P. Strick prepared this case. 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.

The Pharmaceutical Industry

In 2000, the pharmaceutical industry was in a state of adjustment. Growth in the elderly population in the U.S. and increases in life expectancy were projected to strengthen the demand for healthcare products and services going forward, especially demand for prescription medicines. Global pharmaceutical sales were expected to reach $360 billion in 2000, up 8% from 1999.[1] According to Standard & Poor's projections, pharmaceutical expenditures in the United States were expected to grow at an annual rate of nearly 11% between 2002 and 2006. Despite the market's growth, however, many top-selling drugs were coming to the end of their patent lives and would soon face generic competition.[2] Between 2001 and 2005, branded drugs with total annual sales of roughly $35 billion were expected to lose patent protection.[3] In addition to patent concerns, pharmaceutical firms faced price pressure due to escalating demands from government, managed care insurers, and healthcare consumers to lower the cost of prescription medicines.

To protect their market shares, pharmaceutical companies continued to increase the amount they invested in R&D in hopes of yielding more new drugs. Many industry-skeptics, however, were quick to point out that the increase in spending had yet to translate into a dramatic increase in output. Looking at expected output for 2000 and 2001, many of these skeptics worried about a looming "productivity crisis" in the industry. Between 1989 and 1999, pharmaceutical research companies in America invested roughly $185 billion in R&D (adjusted for inflation), spending over $24 billion in 1999 alone compared to sales of $155 billion.[4] **Exhibit 1** shows the historical growth in industry sales and R&D spending since 1970. Exhibit 3 provides data concerning drug-approval activity by the U.S. Food and Drug Administration (FDA) during the 1990s. During this period, the FDA approved nearly 800 new drug applications (NDAs), including 288 new molecular entities (NMEs) (**Exhibit 2**).[5][6][7]

The Drug Discovery and Development Process

Most major pharmaceutical companies followed a similar process in developing new drug products (**Exhibit 3**). First, the company engaged in *pre-discovery research* to identify the drug *target*—a step within a molecular pathway that, when altered, would make a drug effective in treating disease. Once a target was selected, chemists screened numerous compounds—often on the order of one million—to test their ability to bind with the target. A common analogy described the target as a "lock" and the screened compounds as "keys".[8] The goal of the early-stage discovery process was

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[1] Herman Saftlas, "Healthcare: Pharmaceuticals," Standard & Poor's Industry Surveys, December 16, 1999.

[2] Weeks after Eli Lilly's patent for its leading antidepressant, Prozac, expired in August 2001, generic versions took over 80% of the drug's prescriptions.

[3] Herman Saftlas, "Healthcare: Pharmaceuticals," Standard & Poor's Industry Surveys, December 21, 2000.

[4] Pharmaceutical Researchers and Manufacturers of America (PhRMA), *Pharmaceutical Industry Profile 2003*, Washington DC: PhRMA, 2003.

[5] The FDA defines a New Molecular Entity as: "a medication containing an active substance that has never before been approved for marketing in any form in the United States."

[6] US Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), "NDAs Approved in Calendar Years 1990-2003 by Therapeutic Potentials and Chemical Types," <http://www.fda.gov/cder/rdmt/pstable.htm>, accessed June 2, 2004.

[7] Other than NMEs, NDAs are also filed for existing drug substances with, for example, new indications or new formulations.

[8] Gary Pisano, "The Life Sciences Revolution: A Technical Primer," Harvard Business School Note 602-118, 2002.

thus to find keys that matched the identified lock. The most promising compound was referred to as the *lead*; others showing good, but lesser, promise were maintained as back-up compounds.

Lead optimization represented the next phase of discovery. During this stage, the lead would be evaluated in various animal models of disease and its structure would be altered to improve its activity against the target, its ease of entry into the bloodstream, or the duration of its activity. The lead optimization phase also included a series of studies in *pharmacodynamics* (i.e., the way a compound affects the body) and *pharmacokinetics* (i.e., the rate at which a drug is processed by the body). At the end of lead optimization, the company decided whether to select the lead for further stages of clinical testing, thereby making it a drug *candidate*. On average, only 0.2% of compounds initially screened reached the point of *candidate selection*, and the typical elapsed time for compounds to reach candidate selection was four-to-seven years.

Following candidate selection, the prospective drug entered the phase of *preclinical evaluation*. During this period, the drug would undergo a series of additional tests of its toxicity as well as its effectiveness in more detailed animal models of disease. At the same time, chemists studied the appropriate dosage and delivery form (e.g., pill, injectable, etc.) for the drug. The preclinical phase for the average drug lasted one year.

Approximately 60% of the candidates entering preclinical evaluation proceeded to the next stage of development, referred to as *first time in humans* (FTIH), or Phase I clinical trials. In preparation for Phase I trials, the company would file an Investigational New Drug (IND) application with the FDA. Concurrent with this application, the company would develop the detailed protocols required to administer the drug in Phase I trials. Phase I trials tested the safety of the drug on 20 to 80 healthy individuals (i.e., those without the target condition) through a series of pharmacodynamic and pharmacokinetic studies. The Phase I testing of a drug lasted approximately one year.

Seventy percent of the candidates that entered Phase I proceeded to larger Phase IIa clinical trials, which tested the efficacy of the drug in treating the target condition. Such trials would involve between 100 and 500 subjects with the target disease. Phase IIa trials typically lasted one-to-two years.

Only a portion of the candidates beginning Phase IIa were deemed efficacious enough to achieve *proof of concept* (PoC).[9] Achieving PoC indicated that the company believed that the candidate had enough potential to reach the market that it justified the significant investments required for Phase IIb and Phase III clinical trials. These trials, which included between several hundred and several thousand patients with the target condition, aimed to identify the appropriate dosing of the drug and gain a better understanding of its side effects. When relevant, the company might also compare the efficacy of the drug to competing treatments already on the market. These later stage clinical trials lasted an average of two-to-three years. Approximately 50% of the compounds that entered Phase III trials resulted in a new drug application (NDA) with the FDA. Once a drug received FDA approval, it could then be launched, mass-produced, marketed, and sold. The process of FDA review and approval typically lasted 18 months.

The process of discovering and developing a new drug could take anywhere from 10 to 15 years and require more than $240 million in "out of pocket" costs (**Exhibit 3**). Adding the opportunity cost

[9] The standards for achieving PoC differed by firm, and individual firms determined PoC at different points during Phase II trials (e.g., end of Phase IIa versus end of Phase IIb). Nonetheless, most firms required PoC prior to commencing Phase III trials.

of capital and the costs associated with failed projects increased this number to slightly more than $800 million.[10]

Competitive Landscape

At the turn of the century, large firms dominated the global pharmaceutical industry (**Exhibit 4**). These companies employed thousands of scientists each and spent billions of dollars on R&D each year. Their ability to reinvest profits from the sales of their successful drugs allowed them to build pipelines of new drug candidates, which they hoped would produce future blockbusters (i.e., drugs with peak annual sales of at least $1 billion). Since most drugs had an average life of 10 years on the market, pharmaceutical companies were given a short window of opportunity to reinvent (literally) their product portfolio.[11] Due to the high rate of attrition experienced in drug candidates, a larger pipeline offered more chances of producing a blockbuster, putting smaller companies at a disadvantage. As the race for the next blockbuster drug ensued, the pharmaceutical giants continued to expand their pipelines by aggressively seeking mergers and acquisitions (**Exhibit 5**) and by forming research alliances with smaller, specialized firms in the biotechnology sector.

While the "shots-on-goal" approach provided benefits to large pharmaceutical companies, smaller firms specializing in the latest scientific breakthroughs were becoming increasing adept at leveraging their focus. Advances in the knowledge of genetics, molecular biology, chemistry, and computer science were changing the ways in which drugs were discovered. Spawned by university scientists and expatriates from large pharmaceutical firms, thousands of biotechnology companies had formed over the past two decades to commercialize the latest scientific discoveries.

New Technologies

In search of faster, less costly, and more accurate means of discovering new drugs, many pharmaceutical companies were hoping to leverage new technologies. While drug discovery was still a labor-intensive process, human efforts were increasingly being enhanced by more capital-intensive methods, particularly in the earliest stages of pre-discovery research. For instance, using *combinatorial chemistry* techniques, companies were able to synthesize thousands of different chemical compounds systematically from a set number of building blocks. Combinatorial chemistry allowed medicinal chemists to build large "libraries" of drug candidates. The testing process for these compounds also benefited from technological advances and automation. *High-throughput-screening* machines allowed scientists to test (in vitro[12]) up to 100,000 compounds per day against various therapeutic targets.[13]

Besides speeding up drug discovery through automation, companies were also trying to use new technologies and their improved knowledge of molecular biology to focus their research. Rather than just randomly screening compounds in search of a potential "hit", companies were doing *rational*

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[10] Joseph DiMasi, Ronald Hansen, and Henry Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, 2003.

[11] A drug patent granted the patent holder exclusive rights to the drug for 20 years (from the date the patent was submitted), after which time generic versions of the drug could be introduced into the market. If it took roughly 10 years to develop a drug from patent application to FDA approval, most branded pharmaceuticals had roughly 10 years left of patent protection.

[12] "In vitro" refers to tests occurring in a test tube (literally "in glass") and is contrasted to "in vivo" tests that occur in living organisms.

[13] A therapeutic "target" can be a gene, enzyme, or cell receptor believed to be involved in the biological process of a disease.

drug design, essentially starting with a disease target and working backwards to identify lead compounds. With rational drug design, also known as structure-based drug design, a company built a computer model of a disease target and then analyzed the shape and other characteristics that a likely drug molecule should have to properly interact with the target

Pre-Merger Drug Discovery at Glaxo Wellcome and SmithKline Beecham

Glaxo Wellcome and SmithKline Beecham both had rich histories in the pharmaceutical industry, dating back to the late 19th century. Further, both British companies were themselves products of large-scale mergers: Beecham and SmithKline Beckman joined together in 1989 and Glaxo and Wellcome merged in 1995.

While both companies wanted their chemists and biologists to develop new drugs, they also encouraged—to varying degrees—these scientists to publish in academic journals. According to one senior member from Glaxo Wellcome, "Drug discovery and academic research are not mutually exclusive. You can't neglect doing new and interesting experiments. However, you also can't have the attitude that it is enough to do good science and something good will come from it." In fact, one senior scientist from SmithKline Beecham estimated that roughly two-thirds of R&D payroll at both heritage organizations went toward basic scientific research. Scientists at both heritage companies were eligible to receive bonuses, though these incentives were tied to overall corporate performance rather than R&D productivity.

In addition to being encouraged to perform academic research, scientists at both Glaxo Wellcome and SmithKline Beecham held dual reporting relationships as part of both companies' matrix R&D organizations. For example, biologists focused on cardiovascular research would report both to the centralized biology department and to the head of cardiovascular product development. Despite these dual reporting relationships, budgetary authority rested with the centralized functional departments (e.g., biology or chemistry) rather than the therapeutic areas.

Both companies assumed that the responsibility of discovery researchers ended once they had created a candidate compound. Once selected, drug candidates would be sent "over a wall" to a centralized preclinical group. Candidates that successfully completed preclinical evaluation would then be sent to a centralized clinical development group that would advance the compound through human trials and the process of obtaining FDA approval. As head of R&D at SmithKline Beecham, Yamada expressed concern about the transition of compounds from discovery to preclinical development. He remarked:

> At both heritage companies, discovery scientists were evaluated based on how well they produced candidate compounds. There was a clear divide between discovery and development at the candidate selection step. These transitions were difficult. Over 90% of the stuff thrown over the wall from discovery to preclinical development failed to get to market.

A final characteristic of the R&D organization at both heritage companies was a centralized process for making decisions about whether or not to progress projects through the discovery and development pipeline. In both companies, a single committee reporting to the head of R&D made the decisions about progressing compounds. This committee was made up of the senior executives of each line function in the R&D organization, such as genetics research, discovery research, toxicology, clinical pharmacology, preclinical development, clinical development, and regulatory affairs. It met on regular basis, usually monthly, to discuss which projects should be funded and which should be abandoned. Most of the committee members were chosen based on their ability to analyze a

firmwide portfolio of projects and were not specialized experts with respect to any given therapeutic area.

The Planned GSK Merger

On January 17, 2000, Glaxo Wellcome and SmithKline Beecham announced their agreement to merge their firms to create GSK. Their plan was to have the merger completed by the end of July 2000. This merger would create one of the world's largest pharmaceutical companies at that time with an expected market capitalization of nearly $190 billion.

Glaxo Wellcome and SmithKline Beecham, both headquartered in the United Kingdom, had a combined total of nearly 108,000 employees and operations in over 75 countries. In 1999, the two companies had combined revenues and net income of more than $27.3 billion and $4.7 billion, respectively. Over 80% of the combined company's revenue would come from pharmaceutical sales (including vaccines), while the remainder would be derived from consumer healthcare businesses including over-the-counter medicines, oral care products, and nutritional healthcare products. The combined research and commercial capabilities of Glaxo Wellcome and SmithKline Beecham would provide GSK with a substantial presence in a broad range of therapeutic indications. **Exhibit 6** shows the combined pharmaceutical sales of Glaxo Wellcome and SmithKline Beecham by therapeutic area, and **Exhibit 7** shows the sales of the leading products for the two firms. **Exhibit 8** lists historical drug approvals for the two heritage organizations.

The CEDD Proposal

Yamada knew that he needed to move swiftly not only to have the new R&D organization in place by the planned closing of the merger in July but also to prevent enthusiasm for the restructuring from waning. During his initial discussions concerning the CEDD structure, he was impressed by the input of Allan Baxter, the head of Drug Discovery at GlaxoWellcome. He asked Allan to serve as the overall leader of the CEDD initiative.

With Baxter in his new role, Yamada was able to focus on further defining the overall objective of the CEDDs—to create an organizational structure for R&D that combined the strengths of large pharmaceutical firms with those of smaller biotechnology companies. Yamada noted:

> There are times in the R&D process when you want to leverage your scale and there are others when you want to be nimble and responsive. For example, large pharmaceutical companies are very good at the front-end of drug discovery, which often involves capital-intensive, high-throughput screening of compounds for activity against a target. They are also very good at the later stages of drug development—running large clinical trials and managing the FDA approval process. It is in the important middle ground of this process—converting promising compounds into viable products—where the flexibility and responsiveness of smaller biotech firms is essential. The challenge for GSK was to put together an R&D organization that benefited from the best characteristics that big pharma and small biotechs had to offer.

Designing the CEDDs

Yamada had requested Baxter's help because of Baxter's previous work in focusing the drug discovery organization at Glaxo Wellcome. Baxter reflected on this experience:

> When I joined GW, it seemed like any bright idea became a project. Eventually, I counted 59 different diseases that we were pursuing in the discovery organization. We worked to bring this number down to 29. Once we had narrowed the range of diseases, we then tried to select several targets related to each disease and several compounds for each target. If one compound failed, we would have another one right behind it. This way, we were able to learn from prior failures when we tested new compounds.

Yamada asked Baxter to perform a detailed review of the existing capabilities at the two heritage companies with respect to drug discovery. His analysis focused on identifying the number of biologists, by therapeutic area, in each of Glaxo Wellcome's and SmithKline Beecham's discovery laboratories. Baxter noted:

> I focused my initial analysis on the geographic distribution of the biologists rather than the chemists. Medicinal chemists don't need to have a therapeutic focus. If they work on a compound for a kinase in one therapeutic class, chances are they can easily work on a kinase in another therapeutic class. Biologists, however, are more specific to particular therapeutic areas.

Yamada used this analysis to detail a structure centered around six centers of excellence in drug discovery (CEDDs), each focused on a small set of diseases (**Exhibit 9**). These areas were: 1) Neurology; 2) Psychiatry; 3) Anitbacterials and Host Defence; 4) Respiratory, Inflammation, and Respiratory Pathogens; 5) Cardiovascular, Cancer, and Urogenital; and 6) Metabolic, Bone, and Anitvirals. In most cases, therapeutic areas were grouped together based on similarity in known disease mechanisms. For example, many respiratory ailments were known to involve an inflammation response in the body. In some cases, however, therapeutic areas were combined based on the geographic location of researchers. While metabolic and viral disorders did not share similar mechanisms of disease, the majority of biologists involved with both therapeutic areas had been based in Research Triangle Park, North Carolina.

Each CEDD would be led by a senior vice president, who would be selected by Yamada and Baxter. These individuals, many of whom were likely to promoted from within the heritage companies, would be selected, in large part, based on their experience with the "intangible" aspects of drug discovery. Baxter explained, "It is very easy to kill a drug project because no one would ever have proof that you were wrong. Sensing whether or not to *progress* a project is what we will be paying the CEDD heads to do. Their talent will come in knowing when to take chances using gut feeling and experience."

Ideally, each CEDD would contain no more than 350 scientists (**Exhibit 10**). Approximately 250-to-300 of these individuals would be biologists and chemists involved in detailed study of compounds, including their activity in animal and human models of disease. The remaining scientists would be physicians and clinical researchers responsible for designing preclinical and clinical trials of selected candidates. To obtain the desired flexibility and responsiveness, Yamada felt that each CEDD needed to be relatively small, and he set the headcount target based on this belief. He noted that anything larger than that size would risk becoming too bureaucratic and would not allow for day-to-day communication between any two individual scientists within a CEDD. Without this potential for daily interaction, Yamada felt that the value of the CEDDs would be lost.

The small size of the CEDDs would also allow scientists to have different reporting relationships than those in the heritage firms and at GSK's competitors. Yamada observed:

> Almost every drug company has created multidisciplinary R&D teams focused by therapeutic area. That's how drugs are made. The CEDDs, however, will be unique, as they will convert what used to be a matrix into a series of line reporting relationships. In this model, chemists and biologists will no longer report to global functional areas; they will report to the CEDDs.

An essential tool for constraining headcounts would be the establishment of a budget for each CEDD. The R&D Excutive Committee, chaired by Yamada, would be responsible for setting an overall budget for drug discovery (i.e., for all six CEDDs). Allan Baxter would then work with the CEDD heads to allocate these funds based on each CEDD's current pipeline and the expected importance of its specific therapeutic areas for GSK's product portfolio. The leaders of each CEDD then would have full latitude to decide how their respective budgets would be allocated across specific projects.

Each CEDD would identify diseases of interest and would "commission" two centralized research groups—Genetics Research and Discovery Research[14]—to identify targets and lead compounds that act against those targets. Genetics Research would focus on identifying molecular targets, and Discovery Research would use capital-intensive methods, such as high-throughput screening, to identify lead compounds.

This commissioning process, however, would not represent a formal contract. The CEDDs would suggest what they saw as attractive targets to the centralized research groups, but those latter groups would maintain the authority to allocate their resources as they saw fit. Similarly, the CEDDs would not be directly charged for the services of the centralized groups and would not be required to accept any lead compounds that resulted from their suggestions. In addition, the CEDDs maintained the authority to deal with external, as well as internal, parties. For example, the CEDDs would be able to "license in" promising lead compounds from outside firms, assuming that such agreements fell within their budget constraints. The centralized research groups also maintained the ability to "license out" compounds to outside firms for development into drug products. This structure fostered the entrepreneurial spirit that Yamada felt was lacking within the heritage organizations prior to the merger.

As illustrated in **Exhibit 11**, the CEDDs would assume responsibility for projects once they reached the stage of lead optimization. Before that point, projects were the responsibility of the centralized "pre-drug" research groups focused on genetics (composed primarily of biologists) and discovery (composed primarily of chemists).

After receiving a lead compound from Discovery Research, a CEDD would perform the detailed chemical and biological analysis required for lead optimization. In cases where the candidate appeared to be effective against multiple targets, multiple CEDDs could be offered the compound for development with respect to different indications. While the biological evaluation of the lead would be specific to a single CEDD, much of the chemical evaluation performed on the drug would be transferable across CEDDs evaluating the lead for different indications. Yamada expected that between 30% and 50% of the compounds evaluated by *any* CEDD would be evaluated by multiple CEDDs.

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[14] Discovery Research, a centralized department, was distinct from Drug Discovery (i.e., the decentralized CEDDs). Discovery Research was focused on the identification of lead compounds, while Drug Discovery represented the process by which lead compounds were developed into specific drug products.

Upon the conclusion of these tests, the leadership of the CEDD, along with the relevant scientists, would decide whether to progress the compound by selecting it as a *candidate* for preclinical trials in animals. If successful in animal trials, the leadership of the CEDD would then decide whether to move the drug into early-stage trials in humans (i.e., Phases I and IIa).

Through the end of Phase IIa, all progression decisions would be made solely by members of CEDD and would not require review either by Yamada's office or any other centralized board at GSK. This feature would clearly distinguish organizational structure of R&D at GSK from that at other leading pharmaceutical firms where most, if not all, progression decisions required the approval of a centralized R&D committee.

If a compound survived to end of Phase IIa, the leadership of the CEDD would have the option to present the compound to the centralized Development Investment Board (DIB). Presentation before the DIB represented the first point at which corporate-level R&D executives (i.e., those outside of the CEDD) had the ability to make decisions about the progress of specific compounds through the discovery pipeline. The members of this board—executives from both the R&D and commercial organizations within GSK—would solicit information, as needed, from other individuals and would render a final determination on whether the CEDD had achieved proof of concept (PoC) for the compound. The standards for achieving PoC would be highly dependent on the characteristics of the specific compound. For example, the PoC requirements for compounds that addressed "precedented" mechanisms of action (i.e., those mechanisms that were studied in previous trials) were likely to be substantially clearer than those for "unprecedented" (i.e., untested) mechanisms. Ultimately, PoC would imply that a CEDD had provided sufficient evidence of safety and efficacy to justify investment in the expensive, late-stage development of a compound.

Following PoC, a compound would be transferred from the CEDD to a centralized product development group. Product development would be responsible for running Phase IIb and Phase III clinical trials on compounds that achieved PoC. If these late-stage trials, which often involved thousands of patients and costs of more than $85 million, were successful, the product development group would then initiate and manage the process of obtaining final approval from the FDA to market the product.

Given that late-stage product development had historically been separated from drug discovery in both of the heritage organizations, Yamada was reluctant to attempt a significant restructuring of the product development group at the same time he was proposing dramatic changes to drug discovery. Doing both simultaneously might prove too onerous for GSK in the months immediately following the merger. Yamada did, however, note that product development would be governed centrally by a proposed Product Management Board (PMB). While Yamada imagined that the product development organization would continue to be composed of subgroups that focused on particular therapeutic areas—as was the case in each of the heritage firms—the PMB would be responsible for all decisions concerning the progression of compounds from *any* therapeutic area. Yamada felt that these late-stage product development activities needed to be centralized to enable GSK to take full advantage of its scale with respect to Phase III trial design and regulatory affairs.

Incentives

Essential to the successful implementation of the CEDDs would be a significant change in the incentive structure for researchers. In the heritage organizations, discovery researchers were evaluated—but not necessarily compensated—based on the quality and number of targets or leads they identified.

Yamada's goal for the CEDDs was to create incentives that were more closely linked to GSK's objective of creating new medicines. He noted:

> The previous structures at SmithKline and Glaxo provided researchers with a pat on the back for finding targets. Unfortunately, these pats on the back were not accompanied by financial rewards and, not surprisingly, the targets often did not translate into new products. With the CEDDs, we could offer real financial rewards for high quality discoveries. To do this, however, we need to make scientists accountable not just for finding candidates, but for bringing those candidates through PoC. By focusing researchers on particular categories of disease, the CEDDs could make them more responsible for the quality of their work.

To implement this incentive structure, Yamada developed a standard process for reviewing each compound that achieved PoC. For each case, Yamada would appoint a team comprised of four to six middle- and senior-level managers from various parts of the R&D organization, including basic research, preclinical and clinical evaluation, legal and regulatory. This team would exist solely for the duration of this specific review. It would use input from several sources to evaluate the performance of key individuals involved with the research effort. Based on this review, the committee would assign what Yamada referred to as "executive level" stock options to members of the discovery team who made truly outstanding contributions to the project. By assigning options in GSK to key scientists, Yamada aimed to mimic the equity-based incentive structures of smaller biotechnology firms.

In addition to pushing the responsibility of R&D scientists deeper into the development process, Yamada also wanted to encourage the CEDDs to look as widely as possible—whether inside or outside of GSK—for candidate compounds. As a result, the rewards for achieving PoC would not distinguish between internally developed compounds and those obtained via external licensing agreements. The only way in which external compounds differed from their internal counterparts is that the financial commitments associated with in-licensing often had to be approved by central R&D and management committees, as they typically required a one-time increase in a CEDD's budget. Despite this difference, Yamada noted:

> Our goal is to develop innovative medicines, and, to reach that goal, it is important that we do not discriminate between products developed in-house and those that were licensed from other companies. In either case, we will rely on the focused expertise of the CEDDs to help determine which candidates were most likely to translate into important products.

Moving Forward: Implementing the CEDD Proposal

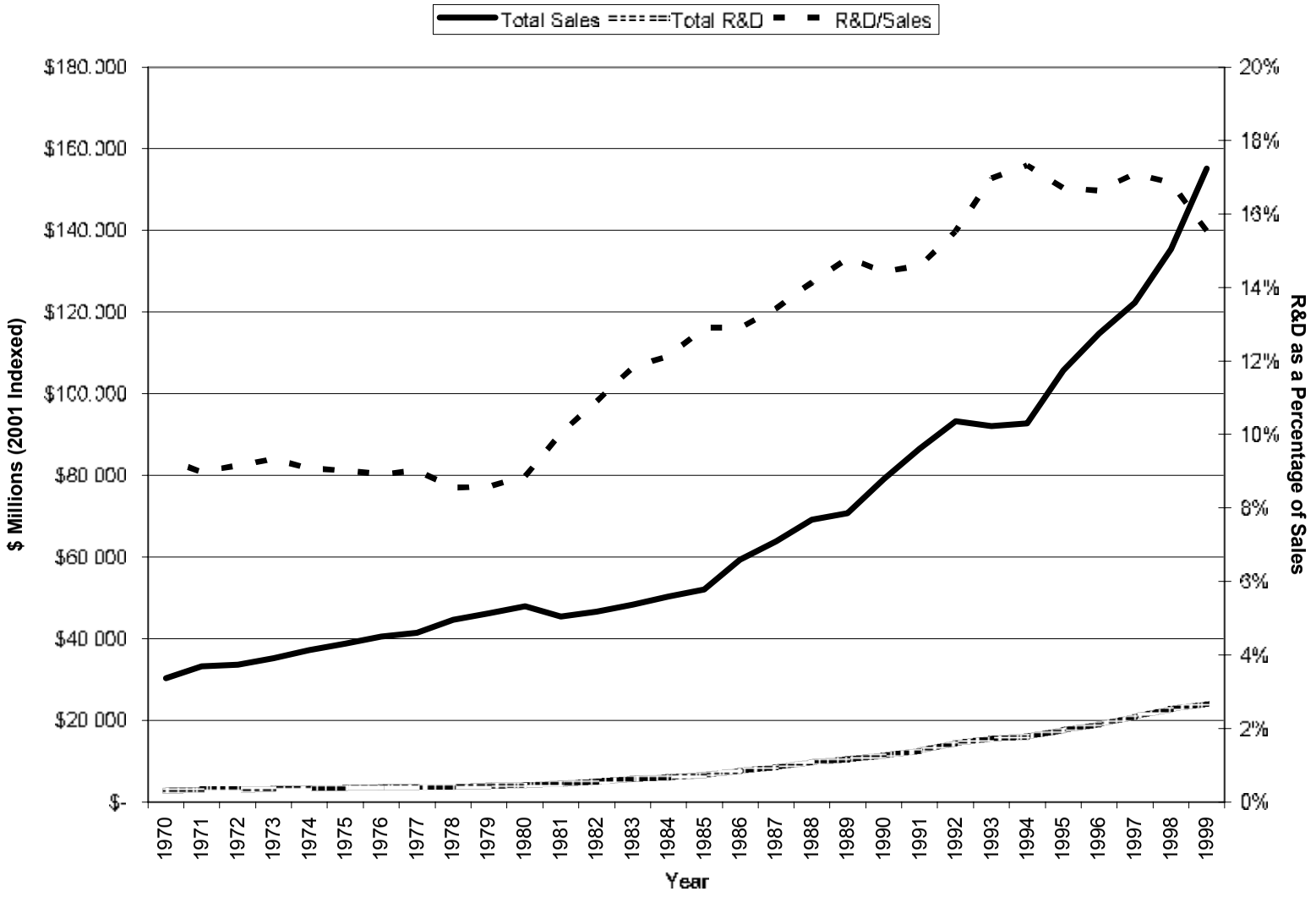
Yamada was pleased by the rapid support he had received for the CEDD concept from both Garnier and the R&D Integration Committee. Nevertheless, he knew that skepticism remained both within and outside of the future GSK organization.

Some inside GSK felt that reorganizing R&D would add to what many expected to be significant overall disruption resulting from the merger itself. They feared that competition between CEDDs would hinder GSK's ability to leverage similarities in "mechanisms of action"—the molecular and biological pathways by which a compound acted against disease—*across* therapeutic areas. For example, it was quite plausible that a compound for the treatment of diabetes might also be an effective therapy against bladder dysfunction. Nevertheless, the planned structure located responsibility for these two diseases in different CEDDs. In a testament to the potential importance of understanding these underlying pathways, one of GSK's major competitors had recently announced its goal of organizing its R&D efforts around major mechanisms of action.

Finally, many felt that reorganizing R&D would not get at the key issue facing the pharmaceutical industry—as more medicines were developed, the remaining disease targets were those that were toughest to understand and attack. Perhaps no level of reorganization would be able to address the future pain created by past successes.

Despite these concerns, Yamada felt that the CEDD structure would bring an important breath of fresh air to the pharmaceutical industry. He noted, "As at every other major pharmaceutical firm, there has always been a clear organizational line drawn, at both Glaxo Wellcome and SmithKline Beecham, between preclinical research and clinical development. The rationale for this break is typically that the former occurs in test tubes and animals while the latter occurs in humans. As a research scientist who also happens to be a clinician, this division has never made sense to me. If our goal is to make drugs for use in humans, that division is not rational. The CEDDs remove this artificial barrier."

Exhibit 1 Pharmaceutical Industry Sales and R&D Expenditures (Domestic and Abroad): 1970 to 1999



Source: Created by casewriter using data from the Pharmaceutical Research and Manufacturers of America (PHRMA), *Pharmaceutical Industry Profile 2004* (Washington, DC: PHRMA, 2004).

Exhibit 2 FDA Statistics, 1991 to 1999

Year	INDs Submitted[a]	NDAs Received[b]	NDAs Approved	NMEs[c]
1999	1,763	139	83	35
1998	2,419	121	90	30
1997	1,996	128	121	39
1996	1,831	120	131	53
1995	1,924	121	82	28
1994	2,156	114	62	22
1993	2,323	99	70	25
1992	2,576	100	91	26
1991	2,116	112	63	30
Total	**19,104**	**1,054**	**793**	**288**
Average	**2,123**	**117**	**88**	**32**

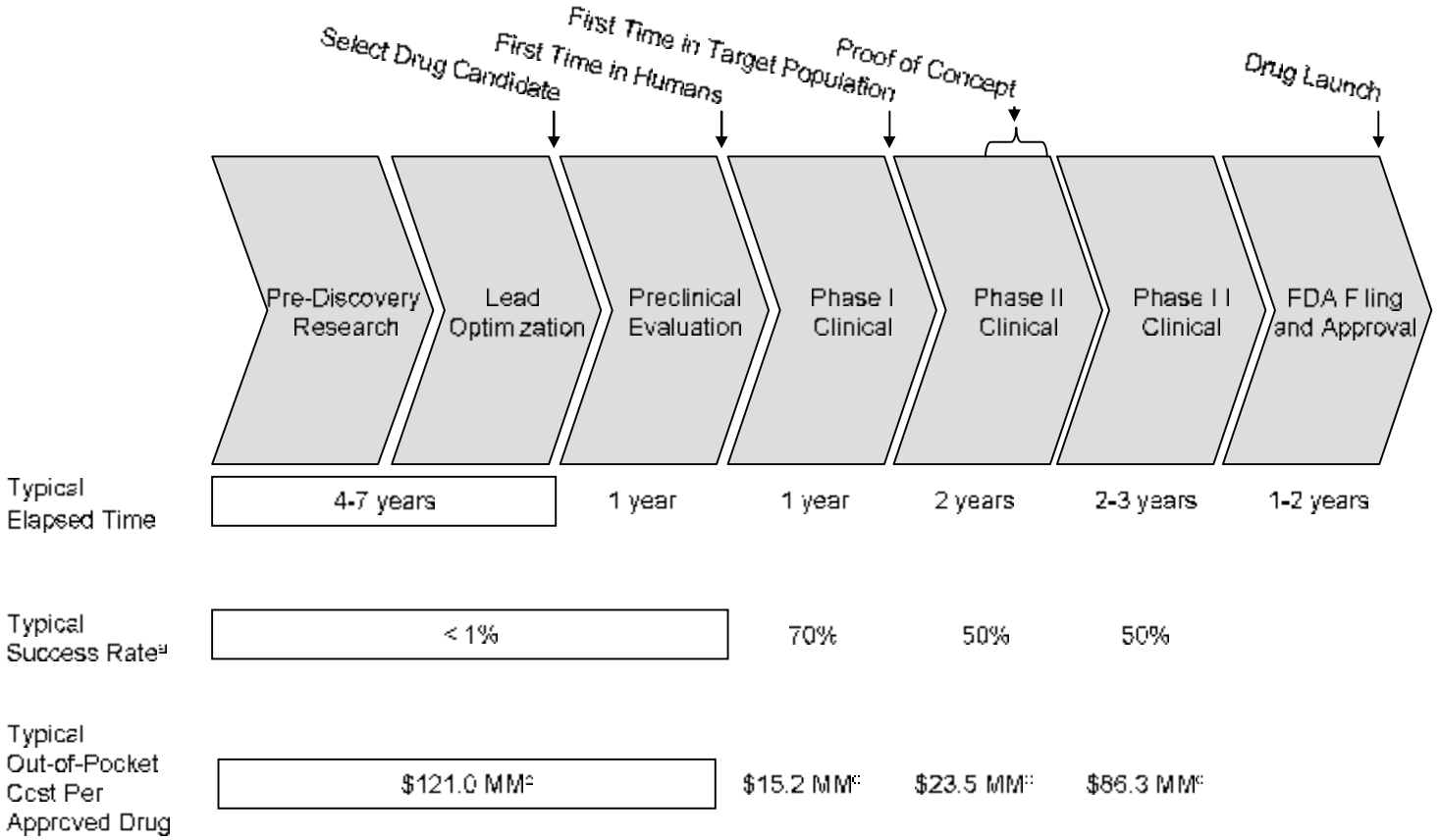
a INDs, or Investigational New Drug filings, are submitted to the FDA for drugs that are starting human testing.

b NDAs, or New Drug Applications, are submitted to the FDA for final approval to market a new drug.

c NMEs, or New Molecular Entities, are medications that contain an active substance that has never before been approved for marketing in the United States.

Source: Herman Saftlas, Standard & Poor's Industry Surveys, "Healthcare: Pharmaceuticals," December 12, 2002.

Exhibit 3 The Process of Drug Discovery and Development



a International Federation of Pharmaceutical Manufacturers Associations, *The Pharmaceutical Innovation Platform: Sustaining Better Health for Patients Worldwide*, 2004.

b Average cost per approved new drug from Gary Pisano, Lee Fleming, and Eli Strick, "Vertex Pharmaceuticals: R&D Portfolio Management," Harvard Business School Case 604-101, 2003.

c "Out of pocket" costs in 2000 dollars, as estimated by Joseph DiMasi, Ronald Hansen, and Henry Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, 2003. The same study listed the "pre-capitalized cost per approved drug" to be $802 million, which accounts for a firm's opportunity cost (cost of capital) and failed research projects.

Source: Created by casewriter using company information, Ernst & Young, "Convergence: The Biotechnology Industry Report," Millennium Edition; International Federation of Pharmaceutical Manufacturers Associations, *The Pharmaceutical Innovation Platform: Sustaining Better Health for Patients Worldwide*, 2004; Gary Pisano, Lee Fleming, and Eli Strick, "Vertex Pharmaceuticals: R&D Portfolio Management," Harvard Business School Case 604-101, 2004; and Joseph DiMasi, Ronald Hansen, and Henry Grabowski, "The price of innovation: new estimates of drug development costs," *Journal of Health Economics*, 2003.

Exhibit 4 End of Year 1999 Financials for Glaxo Wellcome, SmithKline Beecham, and Top Competitors Ranked by Sales ($US Millions)

	Glaxo Wellcome	SmithKline Beecham	Merck & Co.[a]	Novartis	Bristol-Myers Squibb	AstraZeneca	Roche	Pfizer
Sales	13,738.24	13 561.86	32,714.00	21,635.92	20,222.00	18,445.00	18.371 71	16,204.00
COGS	2.472.56	3.409.48	16,763.00	5,540 10	4.861.00	4,968.00	5,083.59	',751.60
SG&A	4,839.94	1.111.68	7,268.20	7,366.81	8.830.00	6,928.00	5,889.28	9,127.00
EBITDA	4,849.65	3.323.71	8,682.80	5,898.31	6.531.00	3,808.00	5,913.97	5,325.40
R&D Exp	2.053.45	1.647.29	2,119.40	2.829.70	1 843.00	2,923.00	2,520.47	2,776.00
Operating Income	4,252.54	2.771.92	7,594.20	4,393.66	5.853.00	2,739.00	4,279.20	4,809.40
Net Income	2.930.50	1.783.22	5,890.50	4,437.81	4.'67.00	1,143.00	3.823.36	3,199.00

a Includes Merck-Medco, a pharmacy benefits management firm with 1999 revenue of roughly $20 billion (Matthew Herper, "Focus on the Forbes 500s: Merck's Venture Fund" www.forbes.com, November 28, 2000, accessed March 25, 2005)

Source: Standard & Poors, Global Vantage

Exhibit 5 Selected Mergers and Acquisitions in the Pharmaceutical Industry (Deal Values Over $10 Billion)

Date Announced	Date Effective	Acquirer Name	Target Name	Ultimate Parent	Deal Value ($US millions)
7/27/1989	10/4/1989	Bristol-Myers Co	Squibb Corp	Bristol-Myers Squibb Co	12,091.00
1/20/1995	5/1/1995	Glaxo Holdings PLC	Wellcome PLC	Glaxo Wellcome PLC	14,284.84
3/7/1996	12/17/1996	Sandoz AG	Ciba-Geigy AG	Novartis AG	30,090.15
12/2/1998	5/24/1999	Sanofi SA(Societe Nationale)	Synthelabo SA(L'Oreal SA)	Sanofi-Synthelabo SA	11,117.67
12/9/1998	4/19/1999	ZENECA Group PLC	Astra AB	AstraZeneca PLC	34,636.78
11/4/1999	6/19/2000	Pfizer Inc	Warner-Lambert Co	Pfizer Inc	89,167.72
12/20/1999	3/31/2000*	Monsanto Co	Pharmacia & Upjohn Inc	Pharmacia Corp.	26,485.96

*Projected effective date

Source: Created by casewriter using data from Thomson Financial, SDC

Exhibit 6 1999 Pharmaceutical Sales by Therapeutic Area (Glaxo Wellcome and SmithKline Beecham Combined) ($US Millions)

Therapeutic Area	1999 Sales	% Of Total
Central nervous system	4,402	20%
Antibacterial	3,856	17%
Respiratory	3,855	17%
Antiviral	2,605	12%
Metabolic and Gastrointestinal	1,434	7%
Vaccines	1,256	6%
Oncology and Emesis	992	5%
Cardiovascular	727	3%
Arthritis	445	2%
Dermatologicals	411	2%
Other	2,055	9%
Total	22,037	

Source: Adapted from Pharmaprojects; Annual Reports.

Exhibit 7 1999 Sales of Largest Products (Glaxo Wellcome and SmithKline Beecham Combined) ($US Millions)

Product	Indication	1999 Sales	Date of U.S. Patent Expiration
Seroxat/Paxil	Depression	2,076	2006
Augmentin	Bacterial infection	1,796	2002
Flixotide/Flovent	Asthma	1,078	2003
Imigran/Imitrex	Migraine	1,057	2006

Source: Adpated from Pharmaprojects; Annual Reports.

Exhibit 8 **Glaxo Wellcome and SmithKline Beecham** Drugs Approved by the FDA, 1990-1999

Year	Drug	Originator	Chemical (C) or Biological (B)
1999	*Agenerase*[a]	Glaxo Wellcome	C
1999	*Relenza*	Glaxo Wellcome	C
1999	*Wellferon*	Glaxo Wellcome	B
1999	*Avandia*	SmithKline Beecham	C
1998	*Amerge*	Glaxo Wellcome	C
1998	*Ziagen*	Glaxo Wellcome	C
1998	*LYMErix*	SmithKline Beecham	B
1997	*Raxar*	Glaxo Wellcome	C
1997	*Requip*	SmithKline Beecham	C
1997	*Teveten*	SmithKline Beecham	C
1996	*Ultiva*	Glaxo Wellcome	C
1996	*Albenza*	SmithKline Beecham	C
1996	*Denavir*	SmithKline Beecham	C
1996	*Hycamtin*	SmithKline Beecham	C
1995	*Epivir*	Glaxo Wellcome	C
1995	*Flolan*	Glaxo Wellcome	C
1995	*Coreg*	SmithKline Beecham	C
1994	*Navelbine*	Burroughs Wellcome	C
1994	*Lamictal*	Burroughs Wellcome	C
1994	*Semprex-D*	Burroughs Wellcome	C
1994	*Serevent*	Glaxo	C
1994	*Famvir*	SmithKline Beecham	C
1993	*Kytril*	SmithKline Beecham	C
1992	*Mepron*	Burroughs Wellcome	C
1992	*Mivacron*	Burroughs Wellcome	C
1992	*Imitrex*	Glaxo	C
1992	*Halfan*	SmithKline Beecham	C
1992	*Paxil*	SmithKline Beecham	C
1991	*Relafen/Relifex*	Beecham Labs	C
1991	*Nuromax*	Burroughs Wellcome	C
1991	*Zofran*	Glaxo	C
1990	*Exosurf Neonatal*	Burroughs Wellcome	C
1990	*Cutivate*	Glaxo	C

[a]Accelerated approval

Source: Adapted from FDC Reports, "Pink Sheets"

Exhibit 9 Planned Distribution of Diseases by CEDD

Neurology **Hub:** Harlow (UK) **Satellite:** Stevenage (UK) **Small site:** Milan (Italy)	**Psychiatry** **Hub:** Verona (Italy) **Satellite:** Harlow (UK)	**Antibacterials and Host Defence** **Hub:** Upper Providence, PA (USA) **Satellites:** Verona (Italy), Harlow (UK), Upper Merion, PA (USA)
Alzheimer's disease Pain Irritable bowel syndrome Acute neuronal injury Migraine Epilepsy Parkinson's disease Multiple sclerosis Satiety	Depression (unipolar) Bipolar disorder Smoking cessation Drug dependency Insomnia Anxiety Schizophrenia Attention deficit hyperactivity disorder	Community acquired bacterial infections Hospital acquired bacterial infections Chemoprotection Malaria

Respiratory, Inflammation and Respiratory Pathogens **Hub:** Stevenage (UK) **Satellites:** Upper Merion, PA (USA), Upper Providence, PA (USA)	**Cardiovascular, Cancer and Urogenital** **Hub:** Upper Merion, PA (USA) **Satellites:** Harlow (UK), Research Triangle Park, NC (USA), Stevenage (UK) **Small sites:** Rennes (France), Les Ulis (France), Tsukuba (Japan)	**Metabolic, Bone and Antivirals** **Hub:** Research Triangle Park, NC (USA) **Satellites:** Stevenage (UK), Upper Providence, PA (USA) Upper Merion, PA (USA), Harlow (UK)
Asthma Chronic obstructive pulmonary disorder Allergic disorders Rheumatoid arthritis Influenza Respiratory syncytial virus Inflammatory bowel diseases Tuberculosis	Atherosclerosis Heart failure Ischaemic heart disease Hypertension Thrombosis Cardiac arrhythmia Cardiac hypertrophy Dyslipidaemia Solid tumours Benign prostatic hyperplasia Chronic renal failure Male erectile dysfunction Pre-term labour Urinary incontinence	Diabetes Obesity Osteoporosis Osteoarthritis HIV Hepatitis B Hepatitis C Herpes Human papilloma virus

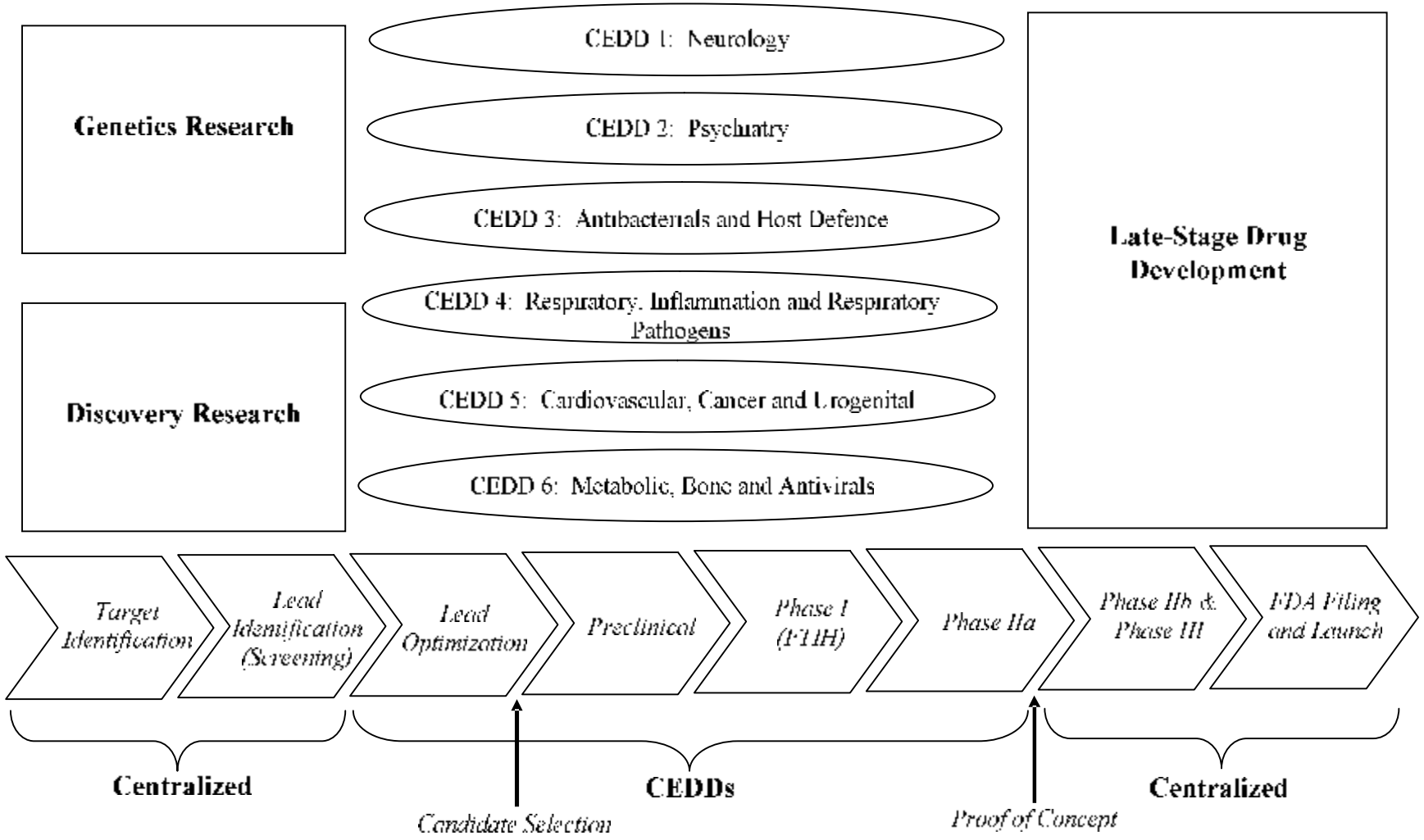
Source: GSK.

Exhibit 10 GSK R&D Scientists by Therapeutic Area (Excluding Genetics Research, Pre-Drug Discovery Research, and Late-Stage Product Development)

Therapeutic Area	Planned FTEs in CEDDs (July 2000)
Antibacterials and Host Defence	275
Cardiovascular, Cancer, and Urogenital	380
Metabolic, Bone and Antivirals	365
Neurology	330
Psychiatry	250
Respiratory, Inflammation, and Respiratory Pathogens	330
TOTAL	**1,930**

Source: GSK

Exhibit 11 Proposed Organizational Structure for GSK R&D



Source: Created by caseworker using company information