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Eli Lilly: Recreating Drug Discovery for the 21st Century

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The rise of personalized medicine is one of the most important developments in health care today. Personalized medicine will change health care almost across the board…but nowhere, I would argue, are the cross-currents of change more powerful or the stakes higher than in the development, manufacture, and sale of prescription medicines. In my industry, we would be powerless to resist personalized medicine, not to say foolish.

— John Lechleiter, President & Chief Operating Officer, Eli Lilly & Co. [1]

Alone in this office on the last working day of 2007, Peter Johnson sighed as he finished reading the rest of the recent talk given by John Lechleiter. It reflected more than five years of deep discussion within Eli Lilly as to how to respond to the strategic challenges facing the industry – a discussion in which Johnson, as Executive Director of Corporate Strategy, had been deeply involved. Johnson was sure that a move to personalized medicine made sense for Lilly and for the patients Lilly aspired to serve, but he was very much aware that implementing the strategy within Lilly was an ongoing challenge with which he wrestled daily. With the move to "tailored therapeutics" now publicly embraced by the senior team and with major investments in place what else, he wondered, could be done to ensure that Lilly's bold move proved to be successful?

Personalized Medicine

2008 found the pharmaceutical industry under increasing pressure. For more than 20 years the industry had been dominated by the discovery of "blockbuster" drugs – drugs that embodied

[1] John C. Lechleiter, "Markets of One: The Pharmaceutical Industry and The Pursuit of Personalized Medicine," speech given at the Conference on Personalized Medicine: A Call to Action, Boston, Massachusetts, November 29, 2007.

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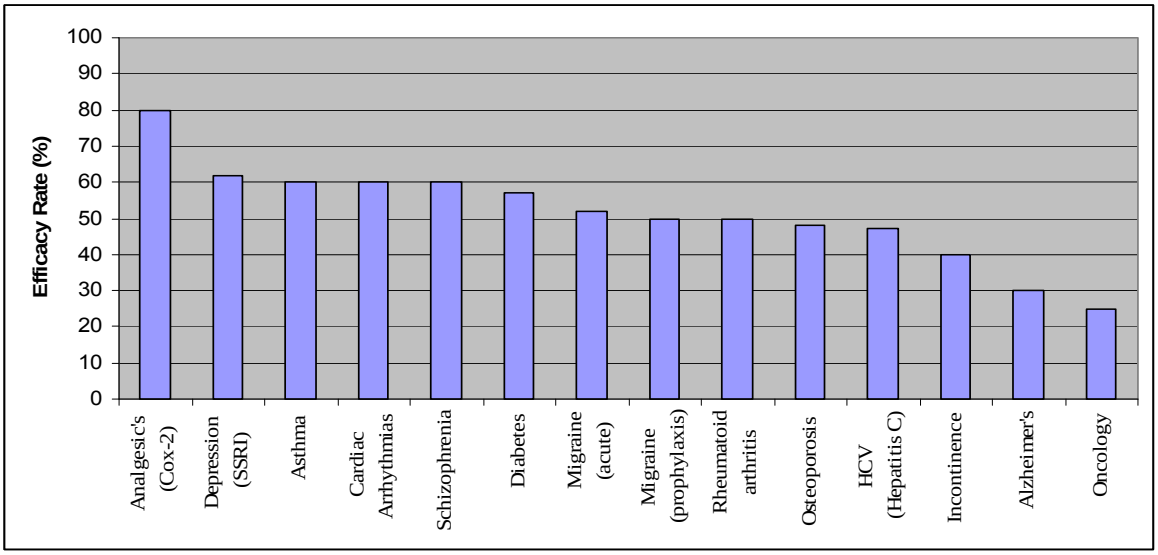
significant advances in medicine, were geared toward the mass market, and sold in the billions of dollars. Plavix, for example, one of the most widely prescribed drugs in the United States, had 2006 sales of $3.2 billion and Lilly's Zyprexa averaged $4.3 billion in revenue over a four year period (2003-2006). Pfizer's Lipitor became the world's first drug to surpass $10 billion in sales in 2004 and generated more than $12 billion in revenues in 2005 and 2006. While these kinds of drugs were hugely profitable, it was proving to be difficult to find replacements for them as they came off patent. Research and development costs were increasing dramatically and rates of new drug introduction had failed to keep pace (**Exhibit 1**). In response, more and more industry observers were suggesting that the industry needed to focus on *personalized medicine*.

There were almost as many definitions of personalized medicine as there were people defining it, but in general the term referred to any therapy that was "tailored" to a particular subset of patients. Physicians and researchers had long been aware that different individuals often react very differently to the same drug. Some studies suggested, for example, that Plavix had almost no effect in as many as 40% of patients for whom it was prescribed. A patient's response to a drug could vary widely depending on factors such as the patient's age, gender, physical condition and phenotype, or genetic makeup. (**Figure 1** shows average efficacy rates for select therapeutic areas.)

Figure 1 Efficacy Rates for Select Therapeutic Areas



Source: Spear B, et. al. Trends in Molecular Medicine, 7(5):201-204, 2001; Eli Lilly internal documents.

Lilly's own research suggested, for example, that the efficacy of one of the company's most promising therapies, Strattera, the only non-stimulant drug approved to treat attention deficit/hyperactivity disorder (ADHD) varied widely depending on the type of patient for whom it was prescribed. In the general patient population, Strattera had a response rate somewhat lower than that of its competitors. However, analysis of clinical trial results indicated that for ADHD patients

with co-morbid anxiety, the response rate to stimulants dropped while the response rate for Strattera stayed the same. Developing a tailoring strategy for Strattera thus had the potential to turn what could be seen as a slight disadvantage in perceived efficacy among the general population into a clear advantage among a target group of patients.

One of the most challenging aspects of developing tailored therapeutics was obtaining a deeper understanding of the factors that drove differences in patient response to particular drugs. Fortunately, while the industry had long understood that segmentation by disease categories and patient groups was often appropriate, the increasing availability of new tools, technologies, and knowledge appeared to have the potential to dramatically expand the potential scope of personalization.

At one end of the scale, researchers were discovering that a particular patient's response might be a function of their genetic makeup. Genentech's Herceptin, approved in 1998 for the treatment of metastatic breast cancer, was one example of a drug that exploited knowledge of a patient's genotype to identify those patients who were most likely to respond to therapy. For patients whose genotype led to the overproduction of a protein called HER2— something that could be determined with the aid of a diagnostic test known as the HercepTest— Herceptin appeared to perform significantly better than common alternative treatments; while for other women the drug performed no better than the standard treatment. Herceptin therefore served a smaller market than a more conventional therapy — by some estimates only 15% to 20% of breast cancer patients — and yet, sales of the drug topped $2.5 billion in 2006. [2]

While genetic profiling was a promising approach in some fields – particularly oncology – there were many conditions for which researchers' knowledge of the link between genetics and therapeutic response was much harder to unravel. In response pharmaceutical firms were increasingly focusing on other kinds of markers as potential differential response indicators. For example, in developing a new compound to treat Alzheimer's, Lilly researchers hypothesized that patients without evident "plaque" — a waxy, translucent substance, composed primarily of protein fibers — were likely to respond very differently to drugs designed to treat the condition than patients with a significant plaque presence. The company was working to develop imaging techniques that would allow it to characterize the plaque status of patients in clinical trials. Roughly 15% of patients with dementia indistinguishable from Alzheimer's did not demonstrate an amyloid plaque burden.

The use of biomarkers of this kind was one tool that was making patient segmentation easier. A biomarker was any biological measurement that provided actionable information regarding disease progression, pharmacology, or safety that could be used as a basis for decision making in drug development.[3] While the concept of biomarkers was nothing new, advanced technology and tools were allowing them to be more pervasive and sophisticated and, thus, to come into play at much

[2] Matthew Bell, "Unraveling the Pharmaceutical Industry," *Arthur D. Little*, 2002.

[3] Julia Boguslavsky, "Biomarkers as Checkpoints," *Drug Discovery and Development*, September 1, 2004.

earlier stages of drug development. By 2006, 90% of Lilly's compounds in preclinical trials had identified biomarkers of some kind.

But biomarkers were just one aspect of personalized medicine. As Lilly's President and Chief Operating Officer John Lechleiter emphasized, "When you understand diversity and the wide spectrum of personalized medicine, then you realize that it has implications in the labs and clinics, certainly…but also in manufacturing, sales and marketing, and all kinds of external relationships."[4] Lilly concluded, for example, that a move to personalized medicine would not only require significant shifts in the way that the firm approached drug discovery and development, but that there would also be significant implications for participants at every stage of the drug delivery value chain. It was likely, for example, that:

- **Patients'** attitudes toward health and how they assessed pharmaceuticals would have great variability, which would require relevant communications about the benefits of tailored therapies.
- **Payers** would expect tailored therapies to demonstrate evidence linking their biomarker/tool result to an actual outcome (e.g., lower cholesterol levels leads to less cardiac events). Moreover, payers (and others with access to longitudinal healthcare data) were likely to have increasingly quicker insights as to whether a treatment was resulting in the desired/promised outcome, which could lead to cost-shifting and risk-sharing if a treatment did not live up to expectations.
- **Providers'** prescribing autonomy would probably continue to be further restricted by payers, and providers might be measured/compensated based upon patient outcomes, which would require that diagnostic/prognostic/monitoring tools be easy to use.
- While in general the **regulatory bodies** were intrigued with the potential of tailored therapeutics, they were likely to operate with caution so as not to risk damage to their reputation if personalized products proved not to be safer and/or more efficacious. Regulators were also likely to be concerned about the potential misuse of tailoring tools and protecting patient privacy.
- **Diagnostic firms** were likely to try and minimize the risk of developing companion diagnostics through actions like seeking access to clinical samples so that they could develop companion diagnostics, and having input into sales promotion efforts. They were also likely to seek pharmaceutical funding for diagnostic development, and — perhaps —broad IP rights on any biomarkers that might be developed.

Personalized Medicine at Lilly: A focus on "Tailored Therapeutics"

With 2006 revenues of $15.7 billion, 41,500 employees worldwide and medicines marketed in 142 countries, Lilly was one of the world's 20 largest pharmaceutical companies. (**Exhibit 2** gives key

[4] John C. Lechleiter, "Markets of One: The Pharmaceutical Industry and The Pursuit of Personalized Medicine," speech given at the Conference on Personalized Medicine: A Call to Action, Boston, Massachusetts, November 29, 2007.

financial information for the firm.) The company, which prided itself on its strong record of science-based research productivity, spent more on R&D as a percentage of sales (20%) than any other major pharmaceutical company. (In 2006 GSK spent 15% and Merck 17%.) It had major research and development facilities in nine countries and conducted clinical trials in more than 60. Lilly's four therapeutic areas included neurosciences (44% of revenue), endocrinology (31%), oncology (10%), and cardiovascular (5%).[5] Zyprexa, a treatment for schizophrenia, bipolar mania and bipolar maintenance, accounted for 28% of Lilly's revenue.

Lilly was one of the only major pharmaceutical companies not caught up in the merger and acquisition activity of the late 1980s and 1990s. (See **Exhibit 3**.) The company was able to safeguard its independence by looking internally for core capabilities it could develop and exploit, including improving speed to market, leveraging existing products, narrowing its R&D focus from eight to five therapeutic areas, spinning off its non-core medical device and diagnostic businesses, and creating multi-functional, product-focused teams (known internally as heavyweight product development teams) which focused exclusively on the development of a single compound. These teams combined all activities related to drug discovery, manufacturing, sales, marketing, and distribution.[6] These activities were complimented by an internal alliance management organization, charged with managing Lilly's external alliances. Alongside remaining independent, partnering was a big part of the Lilly's strategy.

Lilly's strategic shift was coming at a time when several of the company's blockbuster drugs were facing patent expiration. The company expected to lose patent protection on seven products between 2011 and 2013, including Zyprexa, the company's best selling product. Between them the seven accounted for roughly 50% of forecast 2010 revenues. (See **Exhibit 4** for revenue breakdown by product, and **Exhibit 5** for a comparison of results between Lilly and some major competitors.) As a result the company was under significant strategic pressure. One widely cited company goal, for example, was to reduce the cost to develop a new drug from over $1 billion to around $800 million.

Lilly's first public commitment to personalized medicine came in a July 2005 interview, when Lilly's Chairman and CEO Sydney Taurel went public with the company's new strategy telling the *New York Times*, "The challenge for us as an industry, as a company, is to move from a blockbuster model to a targeted model…We need a better value proposition than today."[7] Internally, however, the strategy dated from the summer of 2004 when an internal project known as "Project Resilience" had recommended that the company pursue a strategy focused on what at that time was characterized as a "niche high value" business model. (For a more detailed account of Project Resilience and the strategic thinking that it embodied, please see Sloan Case #07-040, *Eli Lilly's Project Resilience: Anticipating the future of the pharmaceutical industry*.)

[5] Animal Health and "other pharmaceuticals" made up the remaining 7% of revenue.

[6] Matthew C. Verlinden, "Eli Lilly: The Evista Project," *Harvard Business School*, Case No. 699-016.

[7] Alex Berenson, "Blockbuster Drugs Are So Last Century," *The New York Times*, July 3, 2005.

The Project Resilience team described the niche high value strategy as:

> A fully integrated firm that focuses on highly valued niche products. Research efforts focus primarily on targeting therapies to specific subpopulations of patients and capturing those niche opportunities completely with highly effective products. While the total patient number might be smaller, product responsiveness will drive greater market share and premium pricing may be possible for highly effective treatments. Relationships with diagnostic firms are critical to utilize biomarkers and identify the appropriate patients. Marketing messages must focus on identifying the right patient and using a diagnostic and be geared toward B2B capabilities. Buyers will want to ration drug use, particularly of innovative products, so therapies that can identify the right patient will be attractive.

The recommendation followed extensive analysis of the future facing the industry and of Lilly's particular competitive strengths. The Resilience team felt that the niche high value strategy allowed the company to capitalize on its traditional strength in research while giving it some competitive insulation from what was expected to be an increasingly cost conscious world. While the team had considered strategies that might enable the company to thrive in a world in which innovation was much less central to the firm's mission, the senior team had been very reluctant to embrace them. In reflecting on the decision a year later, John Lechleiter recalled "if we had really believed that (a much less innovative world) was the future we would have looked for another option. I couldn't imagine taking the company there…"

Internal reaction to the new strategy was mixed. Lilly's marketing organization was skeptical about the term "niche high value" and its implication that Lilly would be going after smaller markets and, therefore, selling less. Many wondered how the company would make money from the new strategy. Lilly's research organization, Lilly Research Labs (LRL), was further concerned that the Resilience team had put too much weight on a business model and approach that might be appropriate for leading edge cancer therapies but that had little relevance for other therapeutic areas. As one scientist recalled thinking at the time, "You can't just change our business model. You don't know how to do discovery. Furthermore, we have this ongoing pressure to accelerate products to the market." Steve Paul, executive vice president for science and technology and president of Lilly Research Laboratories, was even more direct: "We thought this was biotech b.s. – just another fad."

Targeted Therapeutics

Through 2005 Peter Johnson and his team focused their attention on communicating the importance of the new strategy as an integral part of Lilly's response to the changing pharmaceutical environment. Responding to concerns that the term 'niche' was both misleading and inaccurate, the strategy was renamed "targeted therapeutics." Johnson presented the idea of targeted therapeutics—and the strategic rationale behind it — to over 3,000 Lilly managers as part of the executive program "Leading in Lilly," and to more than 5,000 employees in a series of town hall style talks. A DVD was developed and made available to all Lilly employees on the company's intranet which dealt with questions such as: what drove Lilly to a targeted therapeutics strategy? How does the new strategy fit in with Lilly's strategy overall? How is Lilly implementing the new strategy particularly in R&D and sales and marketing? How do the economics of moving to a targeted therapeutics model work? Sidney Taurel, Lilly's CEO, also took a very active role in advancing the new strategy – presenting it to his board and to over 800 people at Lilly's Global Leadership Conference, and actively talking about its implications throughout the company. These communication efforts were followed up by continual updates to Lilly's board and its top managers.

As **Table 1** below indicates, the targeted therapeutic and the conventional FIPCO (Fully Integrated Pharmaceutical Company) models took very different approaches to R&D, sales and marketing, and manufacturing.

Table 1 FIPCO vs. Targeted Therapeutic Models

Conventional FIPCO	**Targeted Therapeutic FIPCO**
• Large patient populations	• Targeted patient populations
• One size fits all products	• "Customized" treatment
• Few, large products generate majority of revenue	• Many, equally sized products generate most revenue
• Mid-sized R&D portfolio	• Large R&D portfolio
• Dedicated manufacturing focused on few, high volume products	• Highly flexible manufacturing capability
• Primary care, large sales force	• Specialty, technical, smaller sales force
• One size fits all marketing	• Targeted marketing positioning and messages
	• Marketing with companion diagnostic or biomarker
	• Relationships with diagnostics companies
	• Generally lower development costs and improved probability of technical success

Source: Internal Lilly documents.

As with the "niche high value" model, reactions to the targeted therapeutics strategy were mixed. Researchers within LRL took issue with the term "targeted" since they were already focused on trying to find biological targets to guide drug development. "Aren't we already doing this?" was a common response from this group. There was also a feeling in the marketing and sales organization that the company had immediate problems that needed solving before it could worry about transitioning to a new model. As one example, Lilly's potential blockbuster, Xigris, launched in 2001 for the treatment

of sepsis, had 2005 revenues of $214 million, far from the blockbuster mark of $1 billion. Lackluster sales were blamed on the drug's delayed launch and poor efficacy results. As one executive recounted, "The company was trying to find the right language for the strategy. We needed to figure out what we were really talking about when we referred to the term targeting." There also continued to be concern that "targeting" was fine in cases such as oncology in which it was possible to imagine finding a link between an individual's genotype and how they might respond to a drug, but was not a very useful approach in many other cases.

Tailored Therapeutics

As Johnson and his colleagues grappled with these issues they came to the realization that the strategy that they were advocating was best captured using the word "tailored." Lechleiter used an analogy to put the tailored therapeutics strategy in perspective:

> A traditional tailor can sew up some cuffs, extend the sleeves, or even—on very rare occasions—take in the waist. In that same spirit, tailored therapeutics can narrow the target population of patients, tighten up dosing guidance based on various criteria, address the timing of therapy, or provide better information to patients—for example to improve adherence. And, of course, none of these scenarios is mutually exclusive. With regard to the degree of tailoring: There's quite a range between buying whatever's on the rack and ordering a custom made-made suit—just as there's quite a range between 'one-size-fits-all' medicine and truly patient-specific therapies and treatment regimens.[8]

(**Exhibit 6** depicts how Lilly characterizes its ranges of tailoring involving drug discovery and development.)

Intense conversations inside the firm generated the insight that there were many ways in which a drug could be personalized, and that the level of tailoring of any particular drug was likely to vary significantly across the company's four therapeutic areas—neurosciences, oncology, cardiology, and endocrinology. The recognition that drugs such as Insulin had been "tailored" for many years – in that dosage, for example, was carefully calibrated to a patient's blood sugar level – also helped build support for the new strategy. Lilly began to use the model shown in **Figure 2** to illustrate the complete spectrum of potential tailoring opportunities.

Framing things this way made it clear that a tailored therapeutics model was not solely about drug development. It could also include an information delivery system in which the overall message, information provided and language used to market a drug was customized to particular patient populations. A tailored therapeutics model could also include the way information was provided through Lilly's sales force or various e-channels. As Johnson noted, tailoring drug delivery could

[8] John C. Lechleiter, "Markets of One: The Pharmaceutical Industry and The Pursuit of Personalized Medicine," speech given at the Conference on Personalized Medicine: A Call to Action, Boston, Massachusetts, November 29, 2007.

include giving providers and pharmacies choices as to how they received Lilly products, including the size and shape of pills and how they were packaged. It could also include tailoring messages. Johnson explained:

> For example, different cultures have different approaches, attitudes and beliefs about healthcare and medicine, and it is important to speak to these communities in ways that are meaningful to them – and one size fits all messages and information don't do that. Our desire is to identify those patients that have the highest probability of being helped by any of our medications, as well as to identify those who may have a higher probability where the medication will not work either because they are non-responders or because they may have a higher likelihood for a particular side effect.

Figure 2 Tailoring Scenarios

Tailoring "Drug"	⇨	Engineering therapies with a specific patient subpopulation in mind
Identifying "Patient" best suited for drug ➢ Special case	⇨ ⇨	Identifying those patients for whom benefits outweigh risks Identifying responders for targeted therapies (essentially highly tailored therapies)
Tailoring "Dose"	⇨	Optimizing dosing regimen for patient subpopulation(s) to achieve optimal benefit/risk
Tailoring "Time"	⇨	Identify the time to intervene during disease progression, the time to complete therapy, or the time to alter treatment regimen
Tailoring "Information/Tools"	⇨	Accommodate information for patient diversity, questions specific to payers or providers, or provide tools to meet needs of customers

Source: Internal Lilly documents.

Identifying and Building Capabilities

As the company educated employees about the new strategy, the process of operationalizing it began. In early conversations the tailored therapeutics strategy had been presented as a significant shift for the company, or as a new "S curve." Thought was even given to creating a separate business unit within the company devoted to tailored therapeutics. As it became clear that the new strategy would require exploring the possibility of tailoring a drug in multiple ways across the value chain, the decision was made to implement tailored therapeutics within the existing organization. As a result, Lilly made few changes to its organizational structure to accommodate the new strategy.

Lilly's organizational structure was fundamentally functional, with research and development structured as a tightly integrated matrix (**Exhibit 7**). Within this context, Lilly put together a strategic team charged with "watching over" the implementation of tailored therapeutics. The team was chaired by Johnson, and included Eiry Roberts, Vice President in charge of early clinical development and Bert van den Bergh, VP of Global Customer Solutions. The team decided to pursue two parallel tracks in supporting the company's transition to the new strategy. The first was to ensure that every team working on a potential new therapy continually considered the potential for tailoring in its plan, while the second was to ensure that each team had access to the capabilities that it needed to execute a tailored strategy.

Integrating "Tailoring" into Drug Discovery and Development

In order to ensure that every team focused on tailoring as a potential option for its drug, the group introduced a "toolkit" designed to infuse the drug discovery and development process at LRL with a focus on the potential for tailoring any particular drug. The toolkit included, among other things, a list of questions for teams to consider when determining a tailoring strategy. These questions included:

- Do you anticipate that patients can be categorized into responders vs. non-responders? Is there a right patient? Wrong patient?
- Is there a known polymorphism that explains a differential response in a general patient population? How might the polymorphism be detected to identify the responder or non-responder patient population?
- Are there plans to use a diagnostic, prognostic or monitoring tool?
- Are there customized information needs for different patient subpopulations?
- Describe if a tailoring approach will have implications for the product label and regulatory authority negotiations.

The toolkit also included a value proposition template which allowed teams to look at the value of their product across various stakeholder groups and the different needs and agendas of those groups, most especially patients. According to Christine Gathers, who was managing the rollout of the tailored therapeutics strategy,

> In the past, thoughts about the value proposition were sometimes disjointed among the various stakeholders. Discovery was all about producing a different and better molecule and getting it registered, while development was focused on the language that payers would require on the label… The value proposition template has gotten people to look at the value across various stakeholder groups and how the different groups have different needs and agendas. The value proposition template has allowed us to put on paper the key attributes and levers that are driving behavior change in these key stakeholders. When there are a lot of unknowns, we go out and talk to the stakeholders.

The value proposition template was developed by a group called the Tailored Therapeutics Stakeholders Group comprised of chairs of all the governance committees: Target Development (TDC), Lead Development (LDC), Product Development (PDC), and Candidate Development (CDC). Gathers explained the importance of having input from all of LRL's governing committees: "We wanted to get people to think in a 10-year time frame so that what you're doing today in TDC impacts what PDC will be doing 10-years from now. There needs to be alignment across all the governance committees."

Each team was responsible for developing a value proposition based on inputs from medical, discovery, new product development, and health outcomes, and ensuring that there was alignment across all functions. A key element supporting tailored therpeutics was to ensure that at every significant review of the drug's progress, the reviewing managers queried team members on both the drug's value proposition and their tailoring strategy. The value template focused teams on several questions, including:

1. The epidemiology of the disease: heterogeneity, stages of progression, factors that influence heterogeneity, common co-morbidities, known biomarkers, known genetic markers, How is response to therapy determined and what treatment applies to which patient? Who is the patient?
2. Current treatment of the disease. Is there a standard of care? Is there an unmet need?
    - Are there patients that do not respond to SOC? Is there a known polymorphism that explains a differential response in a general patient population? Are there patients that cannot take SOC due to side effects?
    - How might polymorphism be detected to identify the responder or non-responder patient population?
    - Who diagnoses and treats patients with this disease and what kind of ancillary support is needed? What will be the primary and secondary endpoints (i.e., biomarker, outcome, etc.) to impact label claim?
3. Learning from Lilly brand teams and affiliates regarding where current products provide the most value, competitive weaknesses.

In addition teams were also asked to determine the value the new molecule provided that made it better than the current standard of care as well as how a tailored approach could provide a competitive advantage. Teams met periodically with the Tailored Therapeutics Stakeholders Group to talk about the value proposition of their tailoring strategy. It was not mandatory that every molecule included a tailoring strategy, but every team could expect questions about potential tailoring at every major review of the drug's progress.

Alongside the list of questions and the value proposition template, the toolkit included the names of internal experts that the teams could call on for advice on topics ranging from value proposition to quantitative pharmacology to diagnostics and biomarker development to sample banking. As Gathers

noted, "We don't want teams to have to search around for the experts. We want to be able to bring the experts to them."

Building New Capabilities

Lilly also set aside roughly $100 million to develop the new capabilities needed to support the tailored therapeutics strategy. Johnson and Roberts decided that the first step in deciding what to fund was to identify the capabilities Lilly would need to build within its R&D, sales and marketing, and manufacturing functions.

Research and Development A cross functional Tailored Therapeutics Review Panel that included the heads of discovery, medical, new product planning, and diagnostics was given responsiblity for identifying and overseeing the building of capabilities within LRL. Integrative informatics and diagnostics were identified as the two capabilities that LRL most needed to build.

Integrative informatics entailed pulling together data generated across various functions and attempting to use it to generate hypotheses as to where tailoring could be applied. As a first step towards building this capability, LRL funded a "tailored therapeutics workbench." Described as a visualization tool, the workbench was designed to help people think about how to look at data across a wider spectrum—including medical, pharmakinetics and discovery—, to observe trends, and generate hypotheses. The workbench was piloted through a study of Lilly's heart drug Prasugrel. As reported in the *Wall Street Journal*, in a 2007 study, Prasugrel outperformed best seller Plavix in reducing heart attacks by 24%. However, Prasugrel led to 32% more episodes of major bleeding over Plavix. Lilly needed to be able to identify the high-risk bleeders, and the pilot workbench supported Lilly's researchers in generating a wide range of hypotheses as to how to do so.[9]

The pilot created such interest that the panel funded six additional workbenches for 2008, some disease state related and some molecular focused. According to Gathers, there was hope that a capability in integrative informatics would spread beyond LRL to other areas of the value chain including marketing and sales, and perhaps health outcomes: "Having access to this information across the value chain will enable us to better generate hypotheses, and to better understand diseases and how patients react to certain drugs."

While Lilly had some diagnostic discovery experience, it had limited development and no diagnostic commercial experience. The company had never marketed a new Rx product with an accompanying diagnostic test nor had it negotiated the price of a product with a health plan based on product utilization by a specific patient population. As of 2006, the company had fee-for-service arrangements with a wide range of companies including small biotechs and large diagnostic companies. Gaps that had been identified with regard to the company's diagnostic capabilities included:

[9] Ron winslow and Avery Johnson, "Lilly's New Drug Tests Well, With a Hitch," *The Wall Street Journal*, November 5, 2007.

- Diagnostic partnerships that provided a virtual capacity that accommodates fluctuating demand and ensured business continuity and general development and specialized technical/process expertise;
- Internal legal diagnostic IP core competency and awareness of how phase-appropriate IP and asset protection strategies impacted options for diagnostic development;
- Stored/banked tissue specimens required to expedite diagnostic registration in late phase drug development;
- Resources required for functional support, esp. legal.

In addition to investments in integrative informatics and the exploration of the development of new diagostic capabilities, Lilly continued to build upon its existing biomarker capability. While people in discovery and medical together decided what biomarkers were necessary for a particular portfolio, LRL's diagnostic and experimental medicine group provided internal experts to each TA to help them develop their biomarker plan.

According to Gathers, building these new capabilities within LRL would not require a dramatic change in how drugs were developed at Lilly. It was more a matter of thinking and working differently: "It is about building new capabilities and approaches to help us think differently. It's about being more broad minded. For example, it means taking a look at what's on the market, determining what's working and what's not, and drumming up new targets as a result of that information. For instance, we will do clinical development more smartly utilizing quantitative pharmacology as a way to identify the right patients for our products."

Sales and Marketing When it came to Lilly's sales and marketing capabilities, the company would require a more "focused and scientifically sophisticated sales and marketing organization" with the capabilities and experience to sell a targeted therapy with a companion diagnostic. Medical and marketing would eventually need to be tightly linked so that the parameters of the market segment could be understood as early in the development life cycle as possible and appropriate marketing strategies and messages developed. As Johnson noted,

> The central sales and marketing organization, responsible for new product planning, will have to start working much earlier with the TAs. In the old model, central sales and marketing did not become significantly involved in the earliest development stages because typically, the majority of what was being developed never reached the market because of technical failures. But despite the high failure rates, we need to get insights from patients, payers and physicians into our development process earlier. It is critical that our clinical trials, and our discovery efforts, are based on a customer's perspective.

Lilly's sales and marketing function loosely advised LRL on its discovery and development efforts but there were no direct reporting links between the two.

Direct-to-consumer advertising would likely continue to be an important marketing tool, with the focus shifting more towards patient-centric educational material about the disease state, the new drug and the diagnostic that helped identify the right patient for the drug. Marketing and sales messages would be less about how a tailored therapeutic was better than competing products and more about how it addressed specific disease states.[10] Sales and marketing would need to develop other capabilities including payer partnerships in health management, early collaboration on product planning with R&D, consumer marketing, evaluation of patient outcomes, relationships with advocacy groups, and customized provider marketing.

According to Johnson, the sales and marketing organization was beginning to adopt a mindset more in sync with a tailored therapeutics strategy: "While the marketing organization continues to want to accelerate our product launches, they are also focused on the need to have the right data at launch. Because of this, our marketing organization is trying to find more and better ways to be integrated with our development organization, so that our clinical trials are providing the data that answers the real world questions of our customers."

Manufacturing Flexibility would be the key capability that Lilly needed to possess when it came to manufacturing. Manufacturing requirements would be less predictable than they were under the traditional FIPCO model and would depend on the number of products and volumes to be produced, potency of the products, mix of large vs. small molecule products, complexity of compound manufacturing, type of distribution to final market.

Stakeholder Challenges

While Lilly's ability to move its strategy forward was heavily dependent on developing the capabilities that were identified, it also depended on if and how various challenges among and between the value chain's stakeholders could be ironed out.

Patients One of the biggest challenges companies like Lilly faced when it came to patients was compliance. Although patient compliance was not a new challenge for pharmaceutical companies, when it came to the value proposition offered by targeted medicine, ensuring that patients took their medications when and how they were prescribed was critical.

The task of getting patients to comply fell largely on the shoulders of pharmaceutical companies, providers, payers, and the government and therefore solving this challenge would require a certain amount of collaboration among them. With the potential advantages targeted therapeutics offered, patients would need to be educated on their benefits and risks. A big component in educating patients would include winning their trust, which had eroded over time. Patient confidentiality and patient rights pertaining to their privacy would also need to be addressed in light of the shift to personalized medicine. Legal assurances would be needed so that insurance companies were not able to use genetic

[10] "Pharma 2010," *IBM Consulting Servies*, 2002.

information to discriminate against people who had a genetic risk for certain health problems.[11] To serve as a role model for the industry, Lilly approved a new HR policy (the second company after IBM to do so) which stated that Lilly would not discriminate against employees based on genetic information. Lilly wanted to ensure that patients felt protected to participate in medical research and also feel comfortable sharing their information with physicians so that they received the best care.

But there were other complex patient-specific hurdles to overcome. As a senior researcher in Lilly's oncology area pointed out,

> There is an issue in determining the boundary between what Lilly does in clinical trials and what is needed for across the board capability building. Tissue banking, for example, will become increasingly important not only for clinical trials but also as a way to help the company build capabilities more broadly. Using tissue banking for multiple uses, however, will require us to get multiple consent forms signed by patients. We need to be able to promise patients that their samples don't end up in the wrong hands and avoid abundant paperwork in order to get consent for samples to fit multiple purposes. The patient empowerment created by available information can actually do more harm than good in certain situation.

Providers Providers would need to be educated on how targeted therapies could work on smaller patient populations and what potential interactions with other drugs might be. Questions remained on who would provide such education and who would pay for it. Alongside getting educated, providers would have to ensure that their clinical information systems would be able to accommodate personal medicine's increased data and networking demands. Personalized medicine would likely increase the use of point-of-care testing. Providers would need to be prepared to either provide these services, which would require additional staffing, or to outsource them.[12]

Payers Payers represented a significant roadblock for both the development and use of targeted medicines due to the fact that reimbursement procedures were geared toward the one-size-fits-all blockbuster model. Many within the industry believed that inadequate reimbursement was a key reason why companies were not developing diagnostic products.[13]

Solving the reimbursement issue would not be easy and payers would have to address a number of questions, including:

- Will therapies be reimbursed only for those patients who are identified, using whatever tests are available at the time, as likely to respond?

[11] "Targeted Therapies: Navigating the Business Challenges of Personalized Medicine," *Deloitte Center for Health Solutions and Deloitte Consulting LLP*, 2006.

[12] Ibid.

[13] Ibid.

- Should all diagnostic tests for all genetic traits that could pose serious safety issues be covered if they are available —or only if the trait is relatively common and the test relatively cost effective? There was concern among payers that the use of expensive tests for large populations would wipe out any potential savings from targeted drugs.[14]
- Should some demonstrated degree of efficacy in the general population be required to justify reimbursement for new therapies?
- Should improved medical education, new IT systems or patient education be covered?[15]

From a payer's perspective, according to market research conducted by Lilly, there were some market dynamics where tailoring would be most valued including where the market involved a disease that was considered very serious, such as cancer; where the cost of choosing the wrong therapy or drug was very high because of the need to treat a disease quickly or because of high safety risks for treating incorrectly; where there were no good treatment options forcing payers to spend a lot of money on ineffective treatments; and, any market where the payers would spend a significant amount of their total budget.

Another challenge that involved payers pertained to patient data. While pharmaceutical companies had access to a lot of patient data prior to a drug's launch, post-launch data on patients including compliance and response rates was held by insurance companies. In order for Lilly's tailored therapeutics model to excel, this dynamic needed to change. As Johnson explained, "The critical information interface is between the pharmaceutical companies and the payers. We are trying to manage a natural tension in the system. Since payers operate at an aggregate level, they are primarily focused on trying to improve the average outcome for the total patient population. One could argue that this leads them to seek to create the greatest benefit for the greatest number. On the other side of this is the individual patient – each of us. Our goal is to improve our individual outcome."

Diagnostic Firms The emergence of targeted medicine was creating some tension between diagnostic companies and pharmaceutical companies. Diagnostic companies put themselves at financial risk by developing a diagnostic for a drug that was years away from market approval, assuming it won approval. Development cycle times and the costs for drugs and diagnostics were quite different: 10-13 years for a drug at a cost of $1 billion compared to 1 to 2 years for a diagnostic at a cost of $1 million to $2 million. The CEO of a diagnostics company described the dilemma faced by many diagnostic firms: "Frequently, you are going to find breakthroughs in smaller companies that don't have the cash resources to be full partners to the pharma companies. There's an imbalance between who can do what. You don't know if there's going to be a big market or a little market

[14] Kathryn A. Phillips, Stephanie Van Bebber and Amalia M. Issa, "Diagnostics and Biomarker Development: Priming the Pipeline," *Nature Reviews/Drug Discovery*, June 2006.

[15] "Targeted Therapies: Navigating the Business Challenges of Personalized Medicine," *Deloitte Center for Health Solutions and Deloitte Consulting LLP*, 2006.

because of the risk of failure of the drug. Pharma will have to subsidize the development of these assays and potential commercialization for those reasons."[16]

Regulatory Body From a regulatory perspective, a lot of work needed to be done to support the emergence of personalized medicine. Along with its mandate of improving the drug pipeline and increasing the safety of new drugs,[17] the FDA's role in encouraging and supporting the development of targeted therapies would need to be more formalized. As one example, historically the agency had regulated the drug and diagnostic industries independently of one another. With more and more co-developed products being developed, however, the FDA would need to be able to review these co-developed products together. Some in the industry were calling for the agency to set up a special division to expedite reviews of targeted therapies for small populations. Additionally, the FDA needed to develop clear guidelines for pharmaceutical companies about the kind of evidence that would be required to support the approval of targeted therapies.[18] Many in the industry complained that the agency's approval procedures had not kept up with the advancement of drug development.

Pharmaceutical Companies To some extent, Lilly's competitors would also play a role in Lilly's ability to move its tailored therapeutics strategy forward. As Lechleiter noted, there needed to be greater collaboration and sharing of information throughout the industry: "One laboratory's discarded failure may be the missing puzzle piece in another lab's effort to understand a particular patient group or disease pathway. The growing transparency around our clinical trials in pharma is a step in the right direction. In 2004 [Lilly] became the first company to disclose results of clinical trials on the Internet. At the time, it was a somewhat frightening step to take but, as others have followed suit, it has not only helped us to learn from each other's work but I think it also has improved our credibility."[19]

The majority of Lily's competitors were certainly experimenting with a tailored therapeutics strategy. Pfizer led the pack with the number of tailored therpeutic-related deals, with a particular focus on bioinformatics (**Exhibit 8**). When it came to looking at the number of tailored therapeutic clinical trials as a percent of total clinical trials, GSK clearly had the most activity. However, bearing in mind that Schering Plough and Bayer ran far fewer clincial trials than their competitors, these two companies were dedicating a notable percentage of their clincial trials to tailored therapeutics (**Exhibit 9**). Meanwhile, as **Exhibit 10** shows, Lilly led in tailored therapeutic trials within its own therapeutic areas.

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[16] Daniel S. Levine, "Getting Personal," *The Journal of Life Sciences*, November 2007.

[17] Kathryn A. Phillips, Stephanie Van Bebber and Amalia M. Issa, "Diagnostics and Biomarker Development: Priming the Pipeline," *Nature Reviews/Drug Discovery*, June 2006.

[18] "Targeted Therapies: Navigating the Business Challenges of Personalized Medicine," *Deloitte Center for Health Solutions and Deloitte Consulting LLP*, 2006.

[19] John C. Lechleiter, "Markets of One: The Pharmaceutical Industry and The Pursuit of Personalized Medicine," speech given at the Conference on Personalized Medicine: A Call to Action, Boston, Massachusetts, November 29, 2007.

Lilly's Vision

In the summer of 2007, Lilly circulated a small brochure to all employees titled "Lilly's Vision." It took an unsual format – after briefly describing Lilly's Vision (**Exhibit 11**), the brochure reproduced a "mock magazine article" from 2020, describing the process that had led Lilly to be listed in the top 10 "most admired companies." In introducing it, Sidney Taurel described Lilly's vision in the following terms:

> *It has many facets…* Ours is a sophisticated and complex business that is facing the most difficult environmental pressures in its history. Thus, this vision can't easily be distilled down to a mere catch phrase or slogan. That said, the vision projects an image of a company that is innovative, collaborative and responsible: that executes well; and above all, that focuses on improving individual patient outcomes…
>
> *It mandates change….* This vision does not replace our brand, our values, or the other foundational elements that make Lilly special. In that respect, it is not new. But clearly, delivering on this vision commits us to thinking and behaving in new ways. Fortunately, we already have momentum in so many of the areas described by our vision. We are making tangible progress toward the very goals we describe. Now we must accelerate our progress.
>
> *We all own this vision's implementation.* Our transformation begins with each of us. It is a huge resonsibility. But it is a phenomenally exciting opporutnity as well.

Next Steps

Johnson watched the sun set over Indianapolis with mixed feelings. Lilly was clearly committed to a tailored therapeutics strategy. But he wondered whether implementation was fast enough? Were there other things that he or the company should be doing to ensure success? What modifications, if any, should Lilly make to the strategy in light of the industry's increasingly plausible move to more disintegrated value chains? Lilly already had extensive experience working in partnerships and with third parties across the value chain. As this mode increased in importance, would it have implications for tailored therapeutics? If so, how should Lilly respond?

Exhibit 1 Trends in Pharmaceutical Productivity

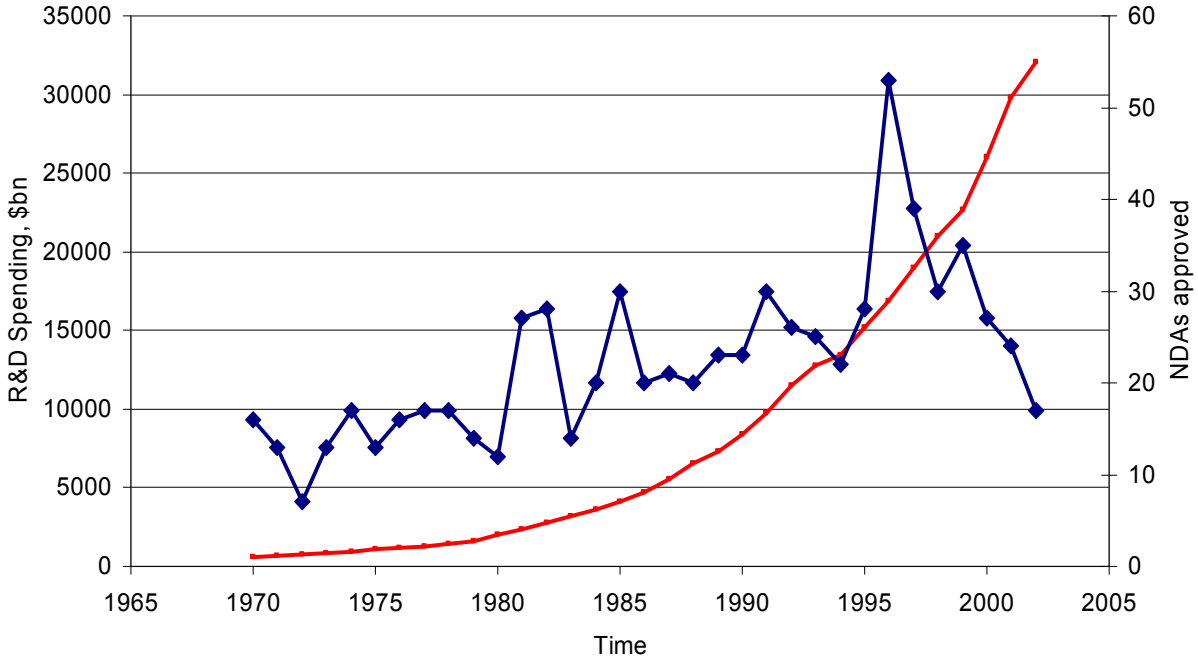


Exhibit 2 Eli Lilly Select Financials, 2002-2006

	2006	2005	2004	2003	2002
Operations					
Net Sales	$15,691.0	$14,645.3	$13,857.9	$12,582.5	$11,077.5
Cost of sales	3,546.5	3,474.2	3,223.9	2,675.1	2,176.5
Research and development	3,129.3	3,025.5	2,691.1	2,350.2	2,149.3
Marketing and administration	4,889.8	4,497.0	4,284.2	4,055.4	3,424.0
Other	707.4	931.1	716.8	240.1	(130.0)
Net Income	2,662.7	1,979.6	1,810.1	2,560.8	2,707.9
Net income as % of sales	17.0%	13.5%	13.1%	20.4%	24.4%
Net income per share-diluted	2.45	1.81	1.66	2.37	2.50
Dividends declared per share	1.63	1.54	1.45	1.36	1.27
Weighted-average number of shares outstanding-diluted (thousands)	1,087,490	1,092,150	1,088,936	1,082,230	1,085,088
Financial Position					
Current assets	$9,694.4	$10,795.8	$12,835.8	$8,768.9	$7,804.1
Current liabilities	5,085.5	5,716.3	7,593.7	5,560.8	5,063.5
Property and equipment-net	8,152.3	7,912.5	7,550.9	6,539.0	5,293.0
Total assets	21,955.4	24,580.8	24,867.0	21,688.3	19,042.0

Segment Information					
	2006	2005	2004	2003	2002
Net sales-to unaffiliated customers					
Neurosciences	$6,728.5	$6,080.0	$6,052.5	$5,554.8	$4,668.3
Endocrinology	5,014.5	4,636.9	4,290.9	3,926.7	3,444.6
Oncology	2,020.2	1,801.0	1,366.2	1,039.8	893.1
Animal health	875.5	863.7	798.7	726.6	693.1
Cardiovascular	514.6	608.9	658.7	669.3	624.9
Anti-infectives	274.6	443.9	478.0	489.9	577.4
Other pharmaceuticals	263.1	210.9	212.9	175.4	176.1
Net sales	$15,691.0	$14,645.3	$13,857.9	$12,582.3	$11,077.5

Source: Eli Lilly Annual Reports.

Exhibit 3 M&A Activity among Top 10 Pharmaceutical Companies

Year	Acquirer	Target	Transaction Value (US$ billions)
1989	Beecham Group PLC	SmithKline Beckman Corp.	$7.9
	Bristol-Myers Co.	Squibb Corp.	$12.1
1995	Glaxo Holdings PLC	Wellcome PLC	$14.3
1996	Sandoz AG	Ciba-Geigy AG	$30.1
1999	ZENECA Group PLC	Astra AB	$34.6
2000	Pfizer	Warner-Lambert Co.	$89.2
	Glaxo Wellcome	SmithKline Beecham	$75.0
2001	Johnson & Johnson	ALZA Corp.	$11.1
	Bristol-Myers Squibb Co.	Dupont Pharmaceuticals Co.	$7.8
2003	Pfizer Inc.	Pharmacia Corp.	$59.5

Source: "The Pharmaceutical Industry: Challenges in the New Century," HBS Case No. 703-489; Securities Data Company; Thomson Financial.

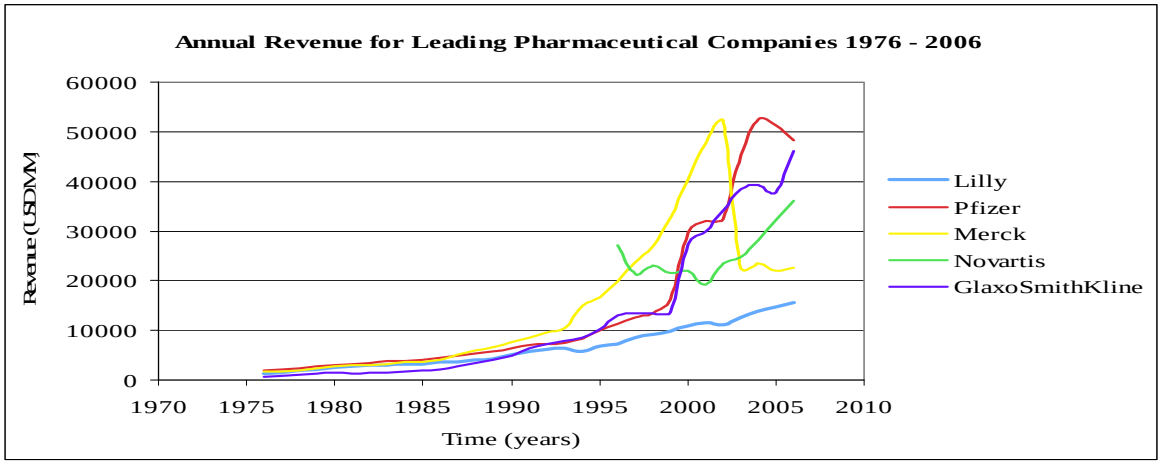
Exhibit 4 Revenue Breakdown by Product

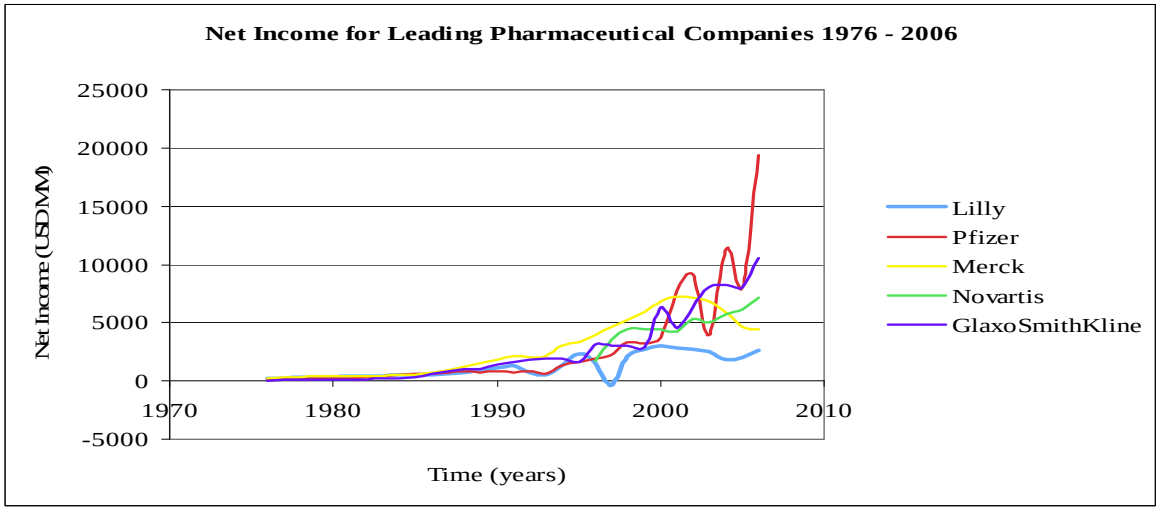
Product	2006	2005	2004	2003	Expiration
Zyprexa	4,363.6	4,202.3	4,419.8	4,276.9	2011
Gemzar	1,408.1	1,334.5	1,214.4	1,021.7	2012
Cymbalta	1,316.4	679.7	93.9	0.0	2013
Humalog	1,299.5	1,197.7	1,101.6	1,021.3	2013
Evista	1,045.3	1,036.1			
Humulin	925.3	1,004.7	997.7	1,060.4	
Animal health products	875.5	863.7	798.7	726.6	
Alimta	611.8	463.2	142.6	0.0	
Forteo	594.3	389.4	238.6	65.3	
Strattera	579.0	552.1	666.7	370.3	
Actos	448.5	493.0	452.9	431.2	
Humatrope	415.6	414.4	430.3	370.9	
Fluoxetine products	315.1	453.4	559.0	645.1	
ReoPro	280.7	296.7	362.8	364.4	
Anti-infectives	274.6	443.9	478.0	489.9	
Byetta	219.0	39.6			
Cialis	215.8	169.9	130.6	73.5	
Xigris	192.2	214.6	201.8	160.4	
Other pharmaceutical	311.0	396.5	485.6	582.5	

products				
Total Net Sales	**15,691.0**	**14,645.3**	**13,857.9**	**12,582.5**

Source: Eli Lilly Annual Reports.

Exhibit 5 Select Financial Data for Leading Pharmaceutical Companies





Source: Eli Lilly analysis from published sources.

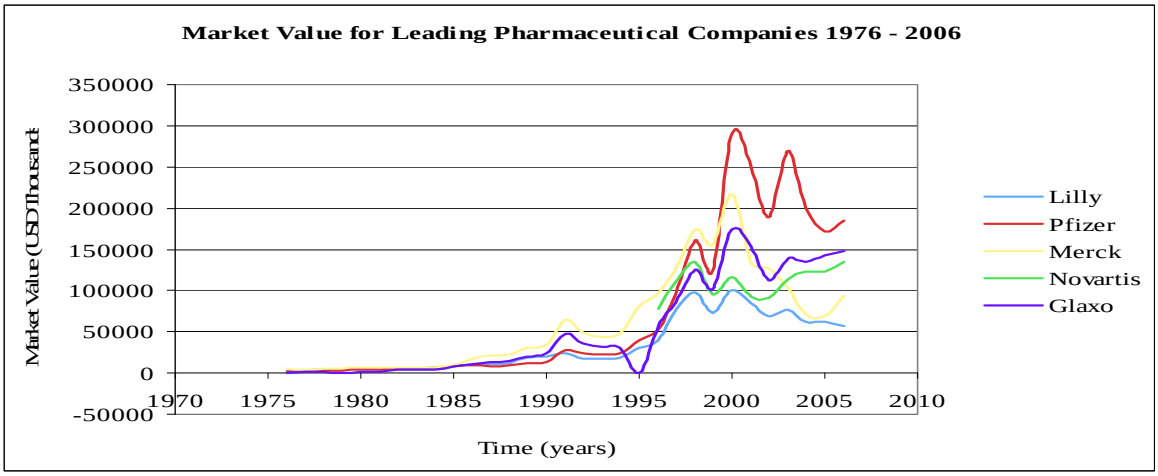


Exhibit 6 Tailored Based Patient Characterization

One size fits all→→→→→→→→→→→→→→Tailoring→→→→→→→→→→→→→→→→Targeted Therapy

Quintile 1

Patients often segmented within market by one or more of the following as perceived by physician observation & evaluation:

- Descriptors (e.g., symptoms)
- Preferences
- Behaviors
- Attitudes
- Differentiation is key

Quintile 2

Patients selected based on one or more of the following:

- Existing co-morbidity
- Patient preference (e.g., delivery device)
- Second line therapy
- Defined point in disease progression (e.g., cut-off points)
- Phenotypic markers which improve response rate but not highly predictive of health outcomes
- Biochemical markers; usually not compound specific
- Symptomatic screening tools
- Differentiation contributes significantly to success

Quintile 3

Characterized by:

- Biochemical, genetic or imaging biomarkers lending to patient stratification
- Biomarkers often not compound specific
- Risk prediction tools
- Outliers identified
- Phenotypic markers that lead to higher responder rate
- Clinical studies often utilize patient enrichment
- Differentiation can be important

Quintile 4

Characterized by:

- Biochemical, genetic or imaging biomarkers that enable capturing more responders, but root cause of disease still not known (i.e., multiple targets exist)
- Phenotypic analysis (clinical or biomarker) that enables capturing more responders
- Individualized dosing based on defined characteristics or response
- May require a companion diagnostic

Quintile 5

Characterized by:

- Existing polymorphism which defines disease or risk of disease
- Well-defined disease phenotype (genetic or biochemical)
- Predictable health outcomes
- Treatment designed to benefit a patient population with poor response to available therapy
- Drug therapy often utilizes a companion diagnostic
- Near term treatments likely to be oncolytics

Exhibit 7 Lilly Organizational Structure

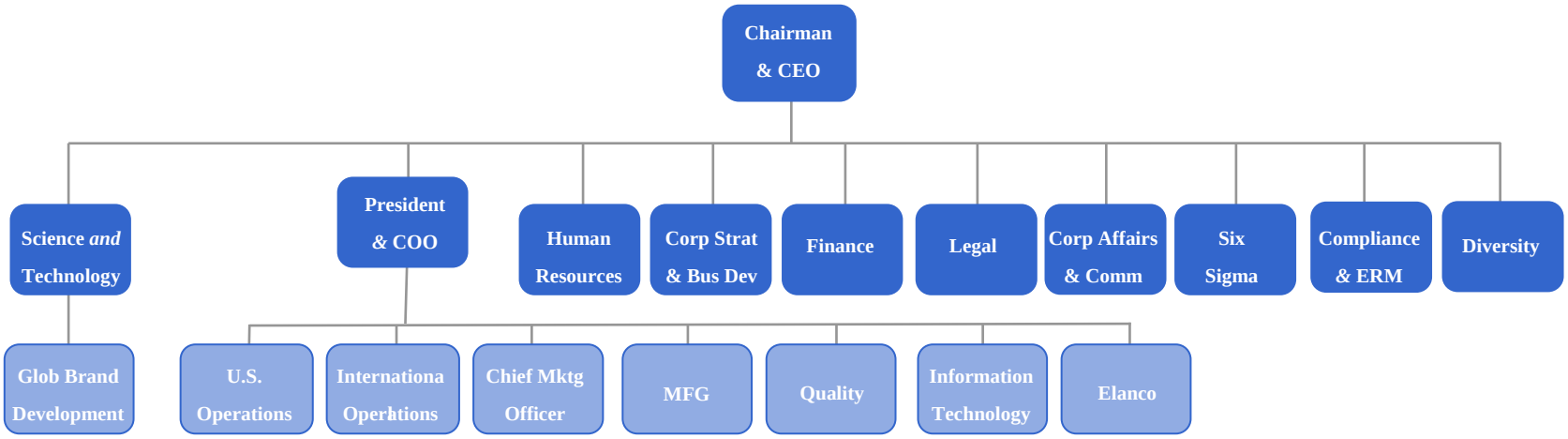
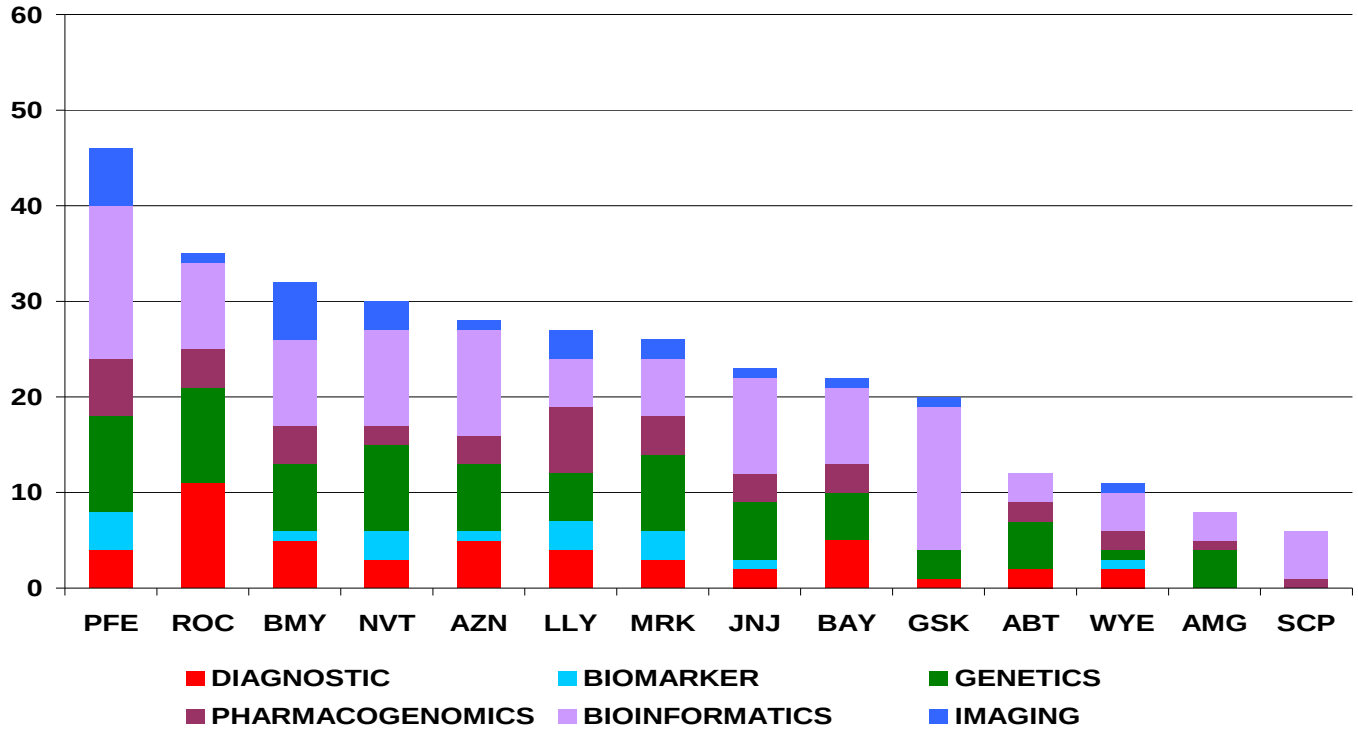
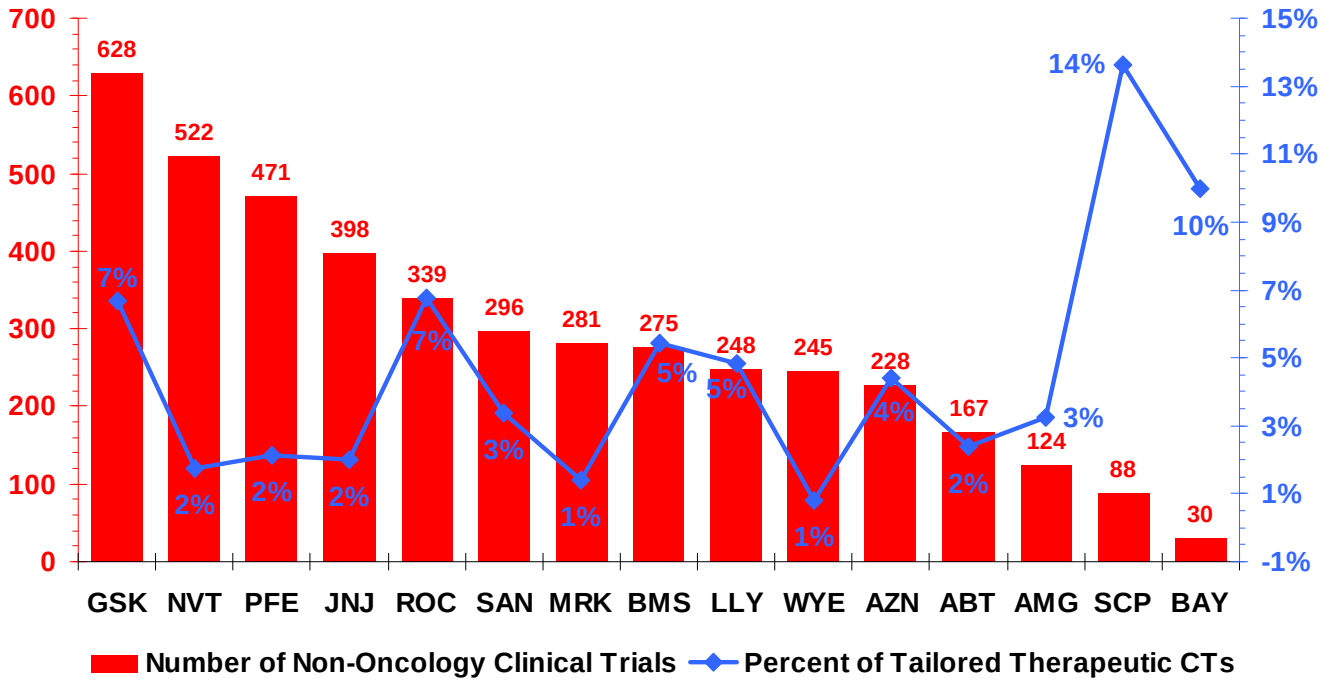


Exhibit 8 Deals by Tailored Therapeutic Technology, 2000-2006



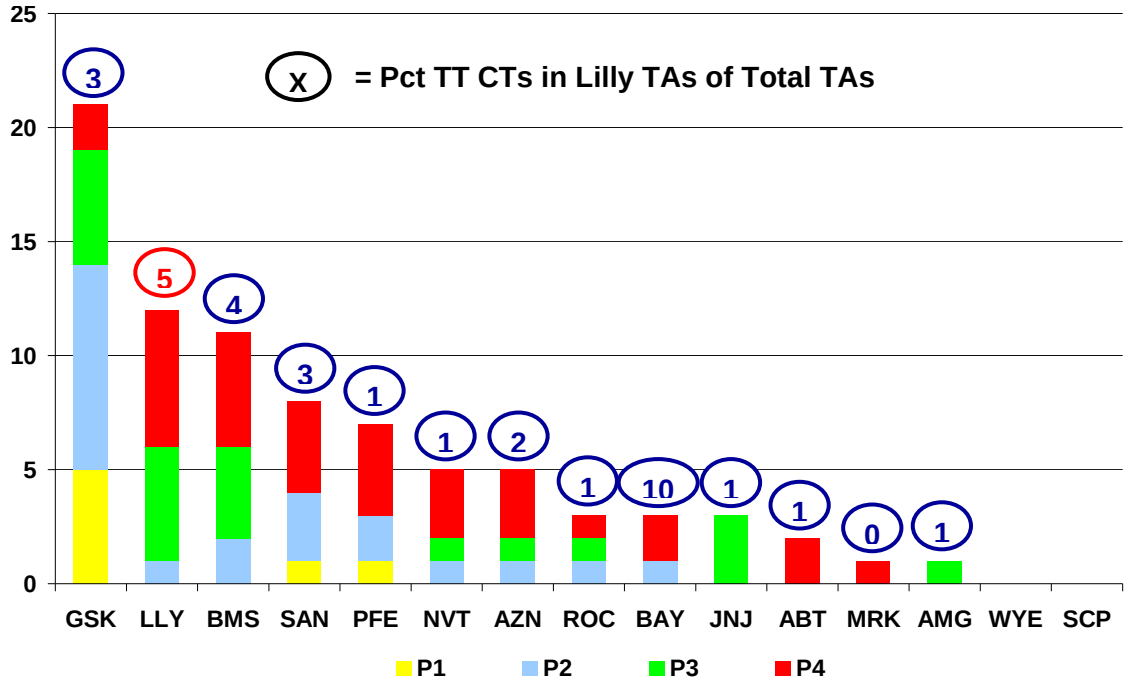
Source: Eli Lilly analysis from published sources.

Exhibit 9 Tailor Therapeutics Clinical Trials as a % of Total Clinical Trials



Source: Eli Lilly analysis from published sources.

Exhibit 10 Clinical Trials for Tailored Therapeutics in Lilly's TAs*



** Exhibit 10 excludes tailoring efforts in oncology as the majority of big pharmaceutical companies are already pursuing a tailored approach in oncology.*

Source: Eli Lilly analysis from published sources.

Exhibit 11 Lilly's Vision

What do we want to accomplish?

Consistent with our values and our brand, how will we lead?

Build relationships with all key constituents – patients, payers, physicians, regulators – to understand what they value

Deliver quality, innovative medicines that improve individual patient outcomes. Tailor medicines for the right patient, delivered in the right dose and at the right time.

Build upon our expertise in therapeutic areas – which today are neuroscience, endocrine, oncology, and cardiovascular – and seize opportunities in other areas.

Combine our deep therapeutic expertise with both our small-molecule and biotechnology capabilities.

Create and integrate external networks to access molecules, capabilities and capacity.

Demonstrate the value of our products in ways that are meaningful to our customers.

Earn the trust and respect of everyone we touch by the way we operate our business and our commitment to patients and society.

Influence our environment to reward innovation.

Hire and develop leaders who are motivated to make a difference in the lives of patients.

Create an agile organization and a culture of inclusion to access the best ideas and capabilities and to reflect the diversity of the patients we serve.

Execute better than our competitors.