Until the mid-1990s, the prescribing preferences of individual physicians collectively influenced the success or failure of new products. While individual physicians continue to be central to a drug’s success, as demonstrated by the enduring number of field-based pharmaceutical sales representatives, they no longer represent decision-making units acting in isolation. Patients and patient advocacy groups, health insurance organizations, pharmacists, nurses and nurse practitioners, regulatory agencies, politicians, and even the media have become active stakeholders in the pharmaceutical market. The pharmaceutical industry’s effort to address growing interest in their products is fueling a growth in Phase IV research funding of over 20 percent each year.¹ Estimates for Phase IIIB and IV spending in 2004 put it at $3.7 billion, and predictions are it will increase to over $5 billion by 2008.²

More Public Awareness

Patients have become increasingly sophisticated and pro-active in their own health care. Internet discussion groups, websites, and patient support groups have all created spaces for patients to come together and learn about their disease and its treatment. For the very committed, resources like Medline, widely available at public libraries, make it possible to follow the results of clinical studies. Direct-to-consumer advertising, which has been allowed on television and radio in the United States since the late nineties, has had an enormous and measurable influence on patients’ desire for and access to certain drugs. Of patients who asked their doctor to prescribe a drug they had seen advertised, 44 percent received it.³

As an increasingly educated community has taken a greater interest in healthcare, the media has taken a leading role in providing relevant information. Health care issues have become big news. Prominent health writers like Jane Brody of the New York Times do their own extensive research into clinical trials and survey medical opinion on a new drug before recommending it to their readers.

A recent story illustrates the power of this trend. The release of results from the Women’s Health Initiative (WHI) study in 2002, a Phase IV trial partially funded by Wyeth and conducted by the National Institutes of Health (NIH) to investigate long-term combination hormone replacement therapy (HRT) for the treatment of cardiovascular and fracture risk in postmenopausal women, generated a significant level of public discussion.⁴ The trial uncovered an association between long-term combination HRT use and an increased risk of breast cancer, generating explosive publicity; in the months after publication of the results, hundreds of stories appeared in U.S. newspapers and magazines addressing the risks of therapy. The publicity surrounding the WHI study is credited with instantly wiping out more than $850 million from the global HRT market.⁵

Not surprisingly, a recently published study found that media reports on the WHI study had a significant influence on women’s use of HRT.⁶ More than 50 percent of women discontinued or curtailed HRT use after reading about the study results, even those
Figure 2. The large number of stakeholders today distinguishes the industry from the past when physicians and drug manufacturers were the primary players in the pharmaceutical industry. Strategic research is now used to address the different information needs of these groups.

using estrogen alone (for which no elevated risk was reported in the study), and those receiving short-term treatment for management of menopausal symptoms (which the study was not designed to investigate).

Today public perceptions of medical treatment can change so quickly and unpredictably that successful companies need to do more clinical research than in the past to remain ahead of the issues. Could additional research focused on short-term HRT have helped women feel more comfortable continuing their therapy? Could data linking termination of treatment for menopausal symptoms with increased incidence of depression, or decreased quality of life, have altered the decisions of women and their physicians?
In the past, physicians were the primary targets of scientific communications. Today, with an increasingly sophisticated public and active media, how pharmaceutical companies choose to address the evolving information needs of new stakeholders through Phase IIIB and IV research can dramatically influence the reception of their products.

**Increased Focus on Drug Safety**

The cost of lawsuits against the pharmaceutical industry has forced many companies to adopt focused risk management strategies at the highest levels. Wyeth’s legal challenges relating to Fenfluramine and Dexfenfluramine (Fen-Phen) have demonstrated how quickly and high pharmaceutical settlements can add up. Costs to Wyeth are now over $20 billion in money either already paid out or set aside to settle ongoing lawsuits.7

Because drug approval represents a balance between protecting public safety and making new products available for patients to use, products are generally approved before their safety profile is fully characterized. Small patient numbers, constraints on patient diversity, and short-term use of therapy associated with Phase II and III studies limit the ability of registration research to detect serious side effects. These unknown side effects may occur in special populations, after prolonged periods of exposure, or with an incidence lower than 1 event per 1000 patients treated. Postapproval studies are therefore necessary to catch unexpected safety events that only emerge when the product is used in a large, diverse population for long periods of time.

The case of spironolactone, a potassium-sparing diuretic, nicely illustrates how results from randomized studies cannot always be generalized beyond the controlled patient populations enrolled. The Randomized Aldactone Evaluation Study (RALES) demonstrated that treatment with spironolactone substantially reduced morbidity and mortality in a controlled population of patients with severe heart failure.9 Not surprisingly, clinical guidelines were amended across the world to reflect this conclusion until, in mid 2004, a Canadian study showed that spironolactone had led to more deaths from dangerously high levels of potassium than would have been expected. With a higher incidence of age- and diabetes-related renal impairment than the study population, more patients in the real world were found to be developing dangerously high potassium levels. Those physicians who continue to use spironolactone now monitor potassium levels much more aggressively.

Recognizing deficiencies in the registration research process, regulators are increasingly demanding post-marketing research as a condition of drug approval. More than 60 percent of FDA approvals in 2003 required at least one post-marketing research commitment as a condition of approval. The FDA register recorded more than 1,479 open post-marketing research commitments as of September 30, 2004.10 As juries increasingly focus on studies

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**Latent Side Effects**

Some side effects reveal themselves only after long periods of exposure to a drug. Lung cancers appear years after patients first start smoking. Mesothelioma usually appears more than 20 years after exposure to asbestos dust. As a less well-known example, in 2004 researchers from Brigham and Women’s Hospital in Boston published data from a prospective study of almost 1,700 women that demonstrated a strong association between frequent acetaminophen use and a 30 percent decline in renal function over an 11-year period. Most drugs in use today have not been available for twenty years, let alone been taken by the same patient for such a long period of time. How many long term side effects will reveal themselves only after decades of patient exposure?8
that could have been done but were not, and public pressure on regulators to focus on drug safety continues to grow, we can only anticipate rapid expansion of Phase IIIB and IV research activities as an important foundation of corporate and public risk management.

**Greater Pharmaceutical Competition**

While the sequencing of the human genome raised widespread hope for a revolution in the prevention and treatment of disease, the beginning of the new millennium has marked a slowdown in novel drug and biologic submissions to regulatory agencies worldwide. While our scientific knowledge has been increasing exponentially, the expanding gap between the laboratory and the bedside has been accompanied by products going off-patent at a faster rate than the industry’s ability to replace them. Faced with escalating costs of drug development and pressure to replenish their patent-protected product portfolios, it has been a safer bet for companies to develop follow-up products to successful drugs than to pioneer truly novel treatments.

While regulators review critical pathways in search of obstacles whose elimination might kickstart a new wave of drug development, the industry faces the growing challenge of differentiating their products in a crowded market of generic alternatives and competing products that share similar approval labels. By generating data to support competitive product positioning through label changes, comparative effectiveness, cost/benefit analysis, and therapeutic guideline development, Phase IIIB and IV research is becoming increasingly important for companies that need to identify and defend product opportunities.

**Increased Focus on Pharmaceutical Pricing**

The pharmaceutical industry in the United States has been the beneficiary of generous policies toward drug pricing. In the world’s largest pharmaceutical market, pricing strategy involves the balance of price against demand to establish an optimal price point. Even so, U.S. health insurance companies, preferred provider networks, and government agencies that are responsible for health costs at both the federal and state level have become ever more sensitive to drug prices. In the United States, the spiraling cost of drugs, particularly for seniors, has become a major political issue.

Other major markets, including Europe, Canada, Australia, and Japan, have adopted a centralized government formulary approach. In these markets, the single buyer is well positioned to negotiate. Pharmaceutical companies must justify a product’s price by demonstrating its potential economic benefits (e.g., decreasing other healthcare costs or

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**Big Opportunities, Big Investment**

Attempts to secure the now $30 billion lipid lowering market have stimulated some of the largest and most expensive Phase IIIB and IV trials in the history of the pharmaceutical industry including LIPID\(^1\) (9,014 patients), MIRACL\(^2\) (3,086), STELLAR\(^3\) (2,268), CARE\(^4\) (4,159), WOSCOPS\(^5\) (6,595), 4S\(^6\) (4,444), AFSCAPS/TexCAPS\(^7\) (6605), HPS\(^8\) (20,536), ASCOT\(^9\) (10,305), CARDS\(^10\) (2,838), ASAP\(^11\) (325), JUPITER\(^12\) (15,000), PROVEIT\(^13\) (4,162), REVERSAL\(^14\) (654), and ALLIANCE\(^15\) (2,442).

These studies, involving more than 75,000 patients, have contributed significantly to our current treatment of high cholesterol and the management of cardiovascular risk, but at no small cost. With industry estimates suggesting a fully loaded cost per patient of between $3,000 and $5,000 in 1999, these trials alone reflect an industry investment in peri- and postapproval research of well over $300m.\(^16\)
increasing work productivity). These market dynamics have created a significant cost differential between products sold in the United States and those sold overseas.

As pharmaceutical competition increases and the incremental benefit associated with new medications continues to diminish, formularies in the United States find themselves in a better position to negotiate prices than in the past. For instance, most formularies now demand generic substitution where available. And as competition increases within therapeutic classes, formularies can negotiate significant discounts when selecting a preferred product. Pharmaceutical subsidy for the aged through Medicare is already increasing collective formulary negotiating power, and the barriers to importation that protect U.S. pharmaceutical sales are under increasing pressure for reform.

In this new world, most pharmaceutical companies recognize a convergence between historic U.S. approaches to pharmaceutical pricing and the cost-benefit rationale successfully applied elsewhere. Cost-benefit-based price justification is already practiced in the United States, and price controls are inevitable at some point in the future.

As the spotlight on pricing grows, drug companies are focusing more energy on research to demonstrate that their products perform differently than inexpensive generics and less expensive competitors. As new treatments emerge for previously undertreated or non–life threatening conditions, companies will find it increasingly necessary to justify the cost of additional treatment against economic benefit.

**Increasing Focus on Health Economics**

Merck’s Phase IIIB Scandinavian Simvastatin Survival Study (4S) was the first to demonstrate that a statin could help save lives and prevent heart attacks in patients with high cholesterol and heart disease. Addressing a group of executives in November 2000, Merck’s chairman, Raymond Gilmartin, responded to concerns about increasing pressure on drug companies to prove the value of their medicines by citing analyses of 4S data which demonstrated that ZOCOR treatment could lower hospitalization rates and reduce the need for costly cardiovascular procedures.28

**Conclusion**

With increasing patient participation in healthcare decision-making, it is becoming more important for pharmaceutical companies to address the gap between the information generated by registration studies and the needs of public and media stakeholders. Phase IIIB and IV research provides a ready tool for such an approach. Regulatory approval was once the final hurdle to product success; today it simply gets the company a seat at the table.

Facing growing pressure to demonstrate value in a crowded market filled with generic competitors, and growing public concern regarding the safety of new medicines, the most effective companies will continue to conduct increasing amounts of strategic research to ensure that their products receive the greatest possible opportunities in a crowded and price sensitive market.

**References**

1. Center Watch, Inc. Presentation at CBI’s 3rd Annual Phase IV Clinical Trials Conference (tracked over the period 1999 to 2001); September 23, 2002.


7. “Pharma Drivers Provide Upside in 3Q Operating Results.” Report on Wyeth prepared by Credit Suisse First Boston, October 20, 2004, p. 3.


27. DataEdge, the King of Research Statistics, Knows How Much You Charge for Research Studies, The Research Roundtable 1999 Sep;1(5).


* Note: All citations to websites listed in this book were verified in May of 2005.