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In Pursuit of Profitability and Effectiveness in the Global Pharmaceutical Industry: Comments on Professor Walker's Four Challenges

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INTRODUCTION

Despite the remarkable pharmacotherapeutic progress of the last half century, no informed person doubts that further advances are desperately needed. Unless they are eradicated by surgery or radiotherapy, most cancers defy cure. AIDS continues to kill. Antibiotic resistance demands replacements for old antibacterials. Many neurologic diseases are poorly treatable, and the cruel deterioration caused by Alzheimer's disease is only slightly amenable to present-day treatment. The list of poorly treatable diseases is long and daunting. Past progress is no guarantee that future progress will take place. The seriousness of the challenges facing the global pharmaceutical industry presented by Professor Walker should not be underestimated, because today's threats to human health are formidable.

A second given is the considerable variation in health care needs from country to country. An African nation might most urgently need an adequate food supply, improved sanitation, and control of malaria-spreading mosquitoes. Switzerland's health care needs would encompass none of these and would stress other objectives. This global diversity in public health and health care needs suggests very strongly that threats to human health implicate far more than the global pharmaceutical industry.

A third given is more uncomfortable—the World Health Organization's idealistic goal of "Health for All by the Year 2000" is honorable but impossible. The "Health for All" rhetoric should not be confused with health facts all over the world. As the global crisis in emerging infectious diseases¹

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1. See David P. Fidler, *The Globalization of Public Health: Emerging Infectious Diseases and International Relations*, 5 IND. J. GLOBAL LEGAL STUD. 11 (1997); Dennis Pirages, *Ecological Theory and International Relations*, 5 IND. J. GLOBAL LEGAL STUD. 53 (1997).

and the growing global tobacco pandemic² demonstrate, populations worldwide face tremendous threats to their health that appear to overwhelm not only financial resources but also political will.

The health of every nation is, however, unquestionably dependent on—among other things—healthy worldwide pharmaceutical and biotechnology industries that are ready, willing, and able to invest large sums of money in the search for and delivery of new drugs, medical devices, and vaccines. Success in these ventures is unpredictable, but failure is guaranteed without commitment of knowledge and resources. (Luck helps, too.) The public's health in the global era is, thus, intimately connected to the health of the global pharmaceutical industry. While discussion of concepts like profitability and efficiency may seem strange against the backdrop of global threats to human health, such discussion is not only important but also critical in evaluating how to fashion responses to global health challenges.

I. THE PROFITABILITY PROBLEM

A fundamental precondition for successful global responses is a profitable global pharmaceutical industry. Professor Walker has aptly described the need for pharmaceutical companies to generate sufficient revenue to fund research and development (R&D) efforts and to provide return on investments to shareholders.³ While traditional U.S. pharmaceutical companies remain profitable for the moment (the new biotechnology industry is another matter and is discussed below), such profitability cannot be taken as a constant. While making profits is a challenging endeavor in any economic sector in today's global marketplace, the profitability problem is particularly acute for pharmaceutical companies that face obstacles in the marketplace, laboratory, and government bureaucracy.

To begin with, the path from discovery of a new therapeutic compound to the marketplace is long and treacherous. Only one in every four or five compounds taken into human subjects receives approval from the U.S. Food and Drug Administration (FDA), and the average time required to gain such approval spans from ten to fifteen years. Professor Walker mentioned efforts

2. Allyn L. Taylor, *An International Regulatory Strategy for Global Tobacco Control*, 27 YALE J. INT'L L. 257 (1996).

3. See Stuart R. Walker, *Global Responses: The Search for Cures in the Development of Pharmaceuticals*, 5 IND. J. GLOBAL. LEGAL STUD. 65 (1997).

being made to reduce regulatory review times.⁴ However, the situation in the United States, at least, is somewhat disturbing.

The FDA has indicated a willingness to facilitate early and continuing collegial discussions between the regulators and the regulated. These discussions are needed to aid the FDA and pharmaceutical companies in reaching agreement regarding the key questions and to help them decide how these key questions should be answered. If such an approach were comprehensively implemented, the final New Drug Application (NDA) could become essentially self-reviewing upon filing.

The available data on recent *ad hoc* conferences between the FDA and the pharmaceutical companies sponsoring NDAs indicate a certain savings in regulatory review time, although no drug has ever been handled in the start-to-finish cooperative manner I have in mind. Such conferences also need an independent appeal mechanism designed to operate in the event of disagreements between the FDA and the pharmaceutical companies; so that, if the FDA is unreasonable in its demands, a pharmaceutical company has a chance to win the argument. Without such an appeal mechanism, a pharmaceutical company is in the position of debating a 600-pound gorilla in his cage.

In addition to the time and expense required for the FDA approval process, the cost of new drug development keeps rising. The average price for the development of a new drug is now well over \$300 million which includes the costs of failures as well as successes. This staggering figure accounts for both out of pocket expenses and the "cost of money," which can best be explained as the amount one could have earned with the money if it were invested so as to yield undelayed earnings (eight to nine percent is the usual level employed for these calculations).

As Professor Walker indicated, cost containment is a key driver of the global pharmaceutical industry today.⁵ However, upward cost pressures also exist, in connection with both the increasing costs of regulatory approval and drug development expenditures in the laboratory, pre-clinical research, and clinical trials. In any industry, cost increases squeeze profitability, unless revenue growth is also enhanced simultaneously by increases in the market's size. As Professor Walker noted, the growth in the global market for pharmaceuticals has slowed dramatically in the 1990s, which underscores the

4. *See id.* at 79-81.

5. *Id.* at 68.

profitability problem for a global pharmaceutical industry that faces increasing costs.⁶

Yet another challenge to profitability is presented by the fact that a new drug is never simultaneously marketed in the three major markets, the United States, Europe, and Japan, despite the progress that has been made in the agreements achieved in the International Conference on Harmonization.⁷ These agreements are designed to create a global dossier approach by eliminating differences among countries in filing formats, requisite data submissions, and the like. As Professor Walker rightly indicates, intergovernmental cooperation on regulatory harmonization is critical for the future welfare of the global pharmaceutical industry.⁸ However, serious transnational differences remain.

Furthermore, given the egos and cultures of regulatory agencies and varying national political pressures, these differences are not likely to yield readily to harmonization. As a result, pharmaceutical companies may have to continue to bear high costs and delayed revenue streams for securing regulatory approvals in the major markets—all of which, again, places stress on the fundamental need for profitability.

An additional problem that ties directly into both the drug development cost and regulatory approval concerns is how little attention has been paid to the quantity of data now routinely collected by pharmaceutical companies and demanded by regulators that could be eliminated without harming the public's health. A multinational team has recently examined the need for carcinogenic studies in rats and mice and concluded that mouse data served no additional usefulness in regulatory judgments over rat data.⁹ This conclusion raises the reasonable question of whether mouse carcinogenicity studies should be routinely performed. To adequately address this problem and perhaps alleviate some of the costs and regulatory burdens on pharmaceutical companies, cooperative dialogue between the industry and the regulators is required on a more substantial basis than currently occurs.

Finally, financial pressures within nations present an obstacle for the pharmaceutical industry. Cost-containment pressures in all countries tend to attack expenditures on pharmaceuticals as a prime target, despite the fact that

6. *Id.* at 66-67.

7. *Id.* at 71-73

8. *Id.* at 81.

9. J.P.J. Van Oosterhout et al., *The Utility of Two Rodent Species in Carcinogenic Risk Assessment of Pharmaceuticals in Europe*, 25 REG. TOXICOLOGY AND PHARMACOLOGY 6 (1997).

drugs represent only a small percentage of any nation's total health care budget. Furthermore, most countries seem inclined to cap the percentage of gross national product spent on health care, including pharmaceuticals, despite the "graying" of the population, which results in a consequent increase in demand and need for health services.

This is an aspect of the health care environment that cannot be addressed solely by changes within pharmaceutical companies. National health care policies in many countries have to be reconsidered—not because they place pressure on pharmaceutical companies but because they may not serve the health needs of the citizenry. The rethinking of national health care policies must take into consideration the views of and pressures facing the pharmaceutical companies.

II. COST EFFECTIVE OR TRULY EFFECTIVE?

One hears increasingly that drugs should be cost-effective in order to justify their use. It is difficult to disagree with this concept in the abstract. However, there is an unwillingness to come to grips with such difficult and painful value judgments as: "How much is a life worth?" "How much is an added year of life worth?" "Is the value of a life different for an eighty year-old than it is for an eighteen year-old?" As far as I can tell, Ceredase, the drug used to treat Gaucher's disease, is being paid for by U.S. insurance plans despite an estimated annual cost of \$75,000 to \$350,000, the average being \$160,000 per year.¹⁰ But what if, rather than a rare disease, Gaucher's disease were a *common* one, afflicting millions of patients?

Nor is it necessarily easy to discern the usefulness of a new product at the time of its launching. Pharmacoeconomic data are increasingly important at the time a new drug is launched because health maintenance organizations (HMOs) and hospital formularies are understandably interested in evidence that a new drug is better, safer, cheaper, or more convenient to take than currently available medications. Those on the demand side of the pharmaceutical market are increasingly under pressure to lower the costs of providing health care, which affects pharmaceutical companies by forcing cost-effectiveness to play a larger role in the rationale for developing new drug

10. Janice M. Hogan, *Revamping the Orphan Drug Act: Potential Impact on the World Pharmaceutical Market*, 26 LAW & POL'Y INT'L BUS. 523, 531 (1995).

compounds. Gone are the days when pharmaceutical companies could spin off slight variations of a developed drug and reap good profits from this practice.

However, the true effectiveness of a new drug may not be apparent until one has the opportunity to study its performance in a “naturalistic” way—in real clinical practice—as opposed to the inevitably different “hothouse” environment of the classical controlled trial, with its restrictive inclusion and exclusion criteria. Compare, for example, the excellent performance of nicotinic acid in lowering serum cholesterol in pre-marketing controlled trials with its disappointing post-registration performance, where its unpleasant side effects are deemed intolerable by perhaps fifty percent of eligible patients. Furthermore, what about a new drug that is uniquely effective for a subpopulation but has little effect on most of the population?

Some new pharmaceutical products will save money, but many will not. What about drugs that “only” make the patient feel better or live longer, without producing a net savings of dollars? Can we agree on a minimal “safety net” level of health care for everyone with the burdensome cost of health care “beyond the net” shared by those willing and able to pay? If so, how are we to predict the number of such subsidizers so that a drug house can decide?

For better or worse, the effectiveness of a new drug has to be evaluated on the basis of the therapeutic contribution it makes to human health, the cost of the drug to health care providers and patients, and the potential size of the market for the drug. Finding new drug compounds that deliver significantly better results in patients, that are cheap to prescribe, and that have a large market to generate adequate revenues will become an increasingly complicated challenge for the global pharmaceutical industry.

III. POSSIBLE SOLUTIONS

How helpful are some of the measures initiated by the pharmaceutical industry to address these problems? Professor Walker discussed the trends toward both horizontal and vertical integration in the global pharmaceutical industry.¹¹ Mergers are logical if they reduce costs, increase productivity, integrate complementary product lines, or guarantee the existence of adequate research budgets to support drug innovation. Otherwise, mergers may only

11. Walker, *supra* note 3, at 68-69.

increase sales temporarily and gladden the hearts of shareholders or stock analysts—a consummation not necessarily high on most people’s priority list in the areas of public health and health care. In addition, the increased size of pharmaceutical companies may in the long run make it more difficult for them to develop the institutional flexibility to respond to all the challenges facing pharmaceutical companies.

As for vertical integration, the purchase of pharmacy benefit management companies (PBMs) by pharmaceutical firms, in theory, could both improve the quality of prescribing practices and cut costs, while augmenting the revenue stream for the acquiring company. However, some have questioned the fiscal wisdom of acquiring some of the bigger PBMs because of their high purchase price and the possibility of ethical conflicts with bad public relations reverberations if the company’s products are substituted for competitor products without scientific justification.

In the laboratory, the promises of combinatorial chemistry, “high throughput screening”, computer-aided drug design, and receptorology are also currently receiving a great deal of attention. To date, however, I believe that these promises, while rational enough, remain for the most part unfulfilled in that they have yet to achieve great advances in either cost control or drug innovation.

The biotech segment of the industry faces its own special problems. It relies heavily on investment capital which is always impatient for rapid return, and it must dampen its euphoria as the ease of the earliest compounds—human insulin, human growth hormone, erythropoietin, and granulocyte colony stimulating factor—have not been matched by success as the industry moves into such unknown territories as septic shock and cancer.

CONCLUSION

Can the drug development process in the global era be made more efficient? How much of the time and money now being spent can be easily eliminated without risking human health? How many of the problems are representative of self-inflicted wounds resulting from company error, and how many represent unreasonable data demands from FDA or other regulatory agencies? Can national regulatory agencies achieve substantial levels of international cooperation to facilitate harmonized and more efficient global regulatory procedures? Will horizontal and vertical integration produce the cost savings desired along with synergy in innovative capabilities? These questions, and

many others, suggest that the future of the global pharmaceutical industry is clouded with uncertainties.

Some of the problems may be inherent in the nature of the business. If the growing complexity and size of NDA filings with the FDA, for example, are occasioned by changes in the state of the pharmaceutical art, then no savings may be possible. However, whether with regard to drug development or the process of drug regulation, it is hard to believe that perfection has been achieved.

Ultimately, the importance of a new drug will be determined not by the novelty of its chemical structure, its mechanism of action, or by the cleverness of the process for picking drug candidates, but by whether it represents an important advance in efficacy, safety, convenience, compliance, and health care cost savings. A "blockbuster" advance should have little trouble achieving heart-warming sales in any developed country plagued by the disease in question. A new drug not so positioned may never pay back the investment required to bring it to market.

The unsolved therapeutic problems facing medicine are not likely to yield to solutions without effective collaboration among scientists in government, academia, and industry, without long-term financial support for biomedical research (both basic and applied), and without adequate return on investment for the innovative sector of the pharmaceutical industry. The sorely needed new products longed for by the sick, their families, and physicians can only be discovered through persistence and commitment of resources. New drug development will probably never be speedy or predictable, but success is no less sweet when achieved despite formidable obstacles.