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# Global Responses: The Search for Cures in the Development of Pharmaceuticals

STUART R. WALKER\*

*In this article, Professor Stuart Walker examines several challenges that will be faced by the global pharmaceutical industry in the near future. These involve the question of improving the overall quality of life and care for millions in an era of cost containment. In order to respond to the increasing demands for advances in medicine while simultaneously retaining an industrially strong, innovative, and resilient economy, responsibility for the necessary changes will need to be shared among governments, the pharmaceutical industry, and health care professionals.*

*In particular, four challenges faced by the global pharmaceutical industry and their responses to each are discussed. The first of these is the need for the industry to secure sufficient revenue from marketed products, so that they may both remain profitable and be able to invest in research and development to facilitate the creation of new medicines. The second challenge arises out of that research and development and involves the production of innovative medicines for the treatment or prevention of diseases for which there is no adequate treatment. Once these new medicines are developed, the third challenge faced by the industry is to bring the new medicines to market in a more rapid and efficient manner. Achieving this third goal is closely intertwined with the final challenge: restructuring the regulation of medicines to ensure the rapid review of new drug applications to get these new medicines to market. Although much remains to be done in achieving these goals, Professor Walker notes that the global pharmaceutical industry is taking decisive steps to approach these challenges and his article operates as a framework for continued progression.*

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## INTRODUCTION

As we approach the new millennium, several global challenges need to be addressed. For example, a number of diseases have either no treatment or inadequate therapies. The World Health Organization's objective of "Health for All by the Year 2000" remains a distant dream, and the overall quality of life and quality of care for the millions of sufferers in the world in an era of cost containment will prove difficult. Commentators have recently stated that the post-millennial economy must be industrially strong, innovative, and resilient in order to respond to the increasing demand for advances in medicines and better health care.<sup>1</sup> The establishment of such capabilities requires that responsibility be shared among governments, the pharmaceutical industry, and health care professionals. In particular, the global pharmaceutical industry faces four basic challenges; namely to remain profitable, to carry out innovative discovery research, to bring new medicines more quickly to the market place, and to ensure that the drug review process is both rapid and efficient. In this article, I review each of these four challenges, discuss the responses of the global pharmaceutical industry to these challenges, and present data to illustrate the outcomes achieved in the pharmaceutical industry to date.

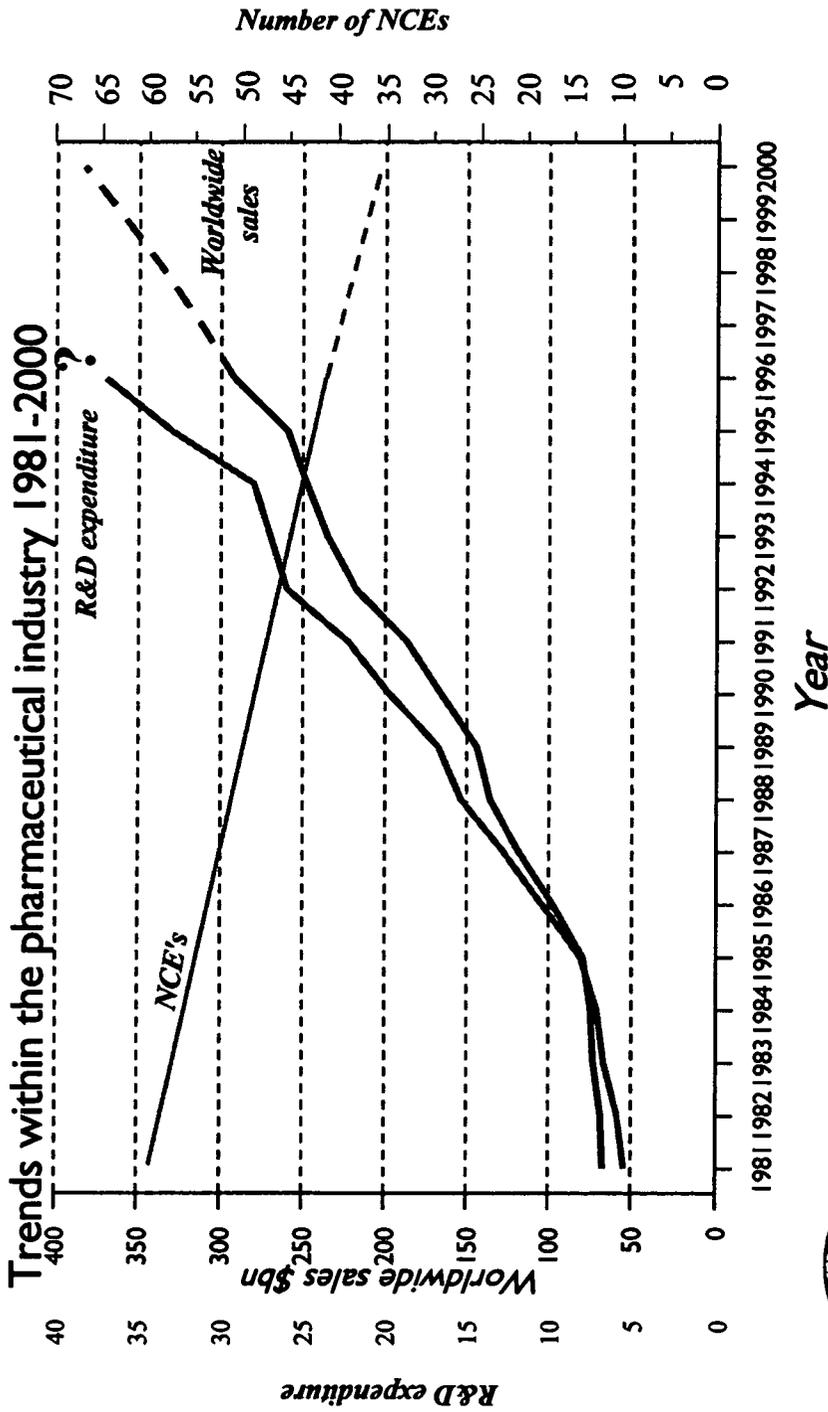
## I. THE PROFIT CHALLENGE

A major challenge for the global pharmaceutical industry is to secure sufficient revenue from marketed products. This involves appropriate investment in research and development (R&D) to ensure the continuous creation of new medicines. This revenue challenge looms large because the expansion of the global pharmaceutical market has slowed down. While global pharmaceutical sales increased annually in the 1980s by double digit figures, as Figure 1 demonstrates, the IMS Strategy Group predicts that sales growth in the latter 1990s will be near seven percent. The estimated global market in 1996 was approximately \$296 billion, with an average of fifteen percent of sales being invested by pharmaceutical companies in R&D. Over the past two decades, R&D investment in the pharmaceutical industry has

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1. Pharma Politics 2000—Key Issues for the Industry: Heinz Redwood Report (1997) (on file with author).

**Figure 1**



Source: CMR International/IMS Pharma Strategy Group

doubled every five years from \$5.5 billion in 1981 to \$45 billion in 1996. The question that needs to be addressed is whether this level of R&D expenditure can continue without an adequate return on the investment. Currently, to get an appropriate price agreement or to make sure that a product is included on a formulary, companies have to not only establish the quality, safety, and efficacy of their products, but also determine the cost-benefit, cost-effectiveness, or the cost-utility of the medicines to be prescribed.

In an era where health care costs are rising because of demand for the highest quality care, the increasing cost of innovative technologies, an ever expanding aging population, and a key interest in assessing patients' quality of life, a large number of government initiatives have been designed to curtail health care expenditures. These initiatives put pressure on prescribers to prescribe generically or less costly innovative medicines, to shift costs to patients by instituting co-payment plans, and to put downward pressure on prices or the profitability of the pharmaceutical industry. The industry's response to these changes has been to: restructure in terms of cost cutting and downsizing, reengineer the drug development process, pursue horizontal integration, and refocus by reexamining the industry's role in the health care delivery system. Health economic studies are just one of the practical aids in decision making and drug selection as purchasers and prescribers endeavor to evaluate "value for money" in health care. Such cost-containment measures directly affect the revenue expectations in the pharmaceutical industry.

Mergers and acquisitions within the global pharmaceutical industry have developed as one of the major responses to the challenge to remain profitable. The 1997 Heinz Redwood report described the mergers and acquisitions of the 1990s as a continuation of the gradual concentration of the research-based pharmaceutical industry that has occurred in periodic bursts ever since the restructuring in 1970 when Ciba merged with Geigy, Warner Lambert acquired Parke Davis, and the Schering Corporation merged with Plough.<sup>2</sup> The next concentrated burst of mergers did not occur until nearly twenty years later in 1989-91, with the mega-mergers of Bristol Myers and Squibb, SmithKline and Beecham, as well as those between Novo and Nordisk, Rhone Poulenc and Rorer, and Sanofi and Sterling Drug. After a brief period of relative calm on the merger front, feverish activity resumed during 1994-96 involving the merger of Glaxo and Wellcome, and Pharmacia and Upjohn, and the formations

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2. *Id.*

of Hoechst Marion Roussel and Novartis (Sandoz and Ciba). In addition, there were significant acquisitions by Roche (of Syntex), American Home Products (of American Cyanamid), Rhone-Poulenc Rorer (of Fisons), and BASF (of Boots Pharmaceutical Division). The most powerful motive of the frequent merger activity in the global pharmaceutical industry in the 1990s has been cost reduction. With slower market growth combined with vigorous cost-containment efforts in health care systems and high levels of R&D expenditures, a competitive premium has been placed on a pharmaceutical company's ability to reduce costs to maintain adequate profitability. Horizontal integration has proved a popular organizational strategy to reduce costs in the pharmaceutical industry.

Vertical integration has been another response of the pharmaceutical industry to the pressure to contain costs. Vertical strategies can involve backward integration into pharmaceutical chemicals, or forward integration into wholesaling or retail distribution of drugs. In the 1990s, however, vertical integration acquired a new meaning; namely the participation of research-based pharmaceutical companies in health care activities. This participation took the form of alliances created when leading research-based pharmaceutical companies, particularly in the United States, purchased Pharmacy Benefit Managers (PBMs) in order to gain experience in prescription management and access to prescription management data. By moving into PBMs, pharmaceutical companies gain "in-house" access to prescription data that will help them to develop disease management schemes.<sup>3</sup> A combination of drug expertise, product development, direct insight into the management of cost containment, and detailed knowledge of prescribing habits and health outcomes should result in integrated pharmaceutical care, which could ultimately benefit patients. In producing horizontal and vertical integration in the global pharmaceutical industry, the pressure of cost containment has led pharmaceutical companies to think and act in new ways to meet the profit challenge. In so thinking and acting, pharmaceutical companies are becoming more keenly aware of the dynamics of health economics, particularly how medicines affect the cost of integrated health care systems that are increasingly cost conscious.

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3. *Id.*

## II. THE INNOVATION CHALLENGE

The second challenge facing the global pharmaceutical industry is to produce innovative medicines for the alleviation, treatment, prevention, or cure of diseases for which there is either no treatment or inadequate treatment available. The research-based pharmaceutical industry's innovative capacity remains its most important attribute. Professor Jurgen Drews, President of International R&D with Hoffmann-La Roche, recently stated that "the most critical factor determining the survival and success of the pharmaceutical industry is its ability to provide novel and economically feasible medicines for the alleviation or cure of serious diseases."<sup>4</sup> The Centre for Medicines Research International (CMR International) has established a marketed medicines database that documents all new chemical entities that have come into the world market over the past twenty-five years. While this database only details new chemical entities, without making any judgment with regard to their innovative value, it does highlight the fact that the global pharmaceutical industry has marketed forty to fifty new molecular entities each year since the early 1970s, giving a total output between 1970 and 1996 of almost 1,300 compounds. As Figure 2 shows, the data suggests that the total numbers have been declining in the past decade, however, there are strong indications that the pharmaceutical industry intends to remain at the cutting edge of innovative research. For example, pharmaceutical companies are examining new and better ways of improving the drug discovery process by means of combinatorial chemistry and high throughput screening, as well as actively exploring new medical treatments including genetic manipulation and gene therapy.<sup>5</sup> In addition, the discarding of the "not invented here" syndrome means that there is a keen interest in forming alliances and collaborations with government organizations and academic institutes. There is also an interest in forming alliances with inter-company collaborations such as those developed in the 1990s in the field of AIDS research and those starting to develop in connection with malaria.

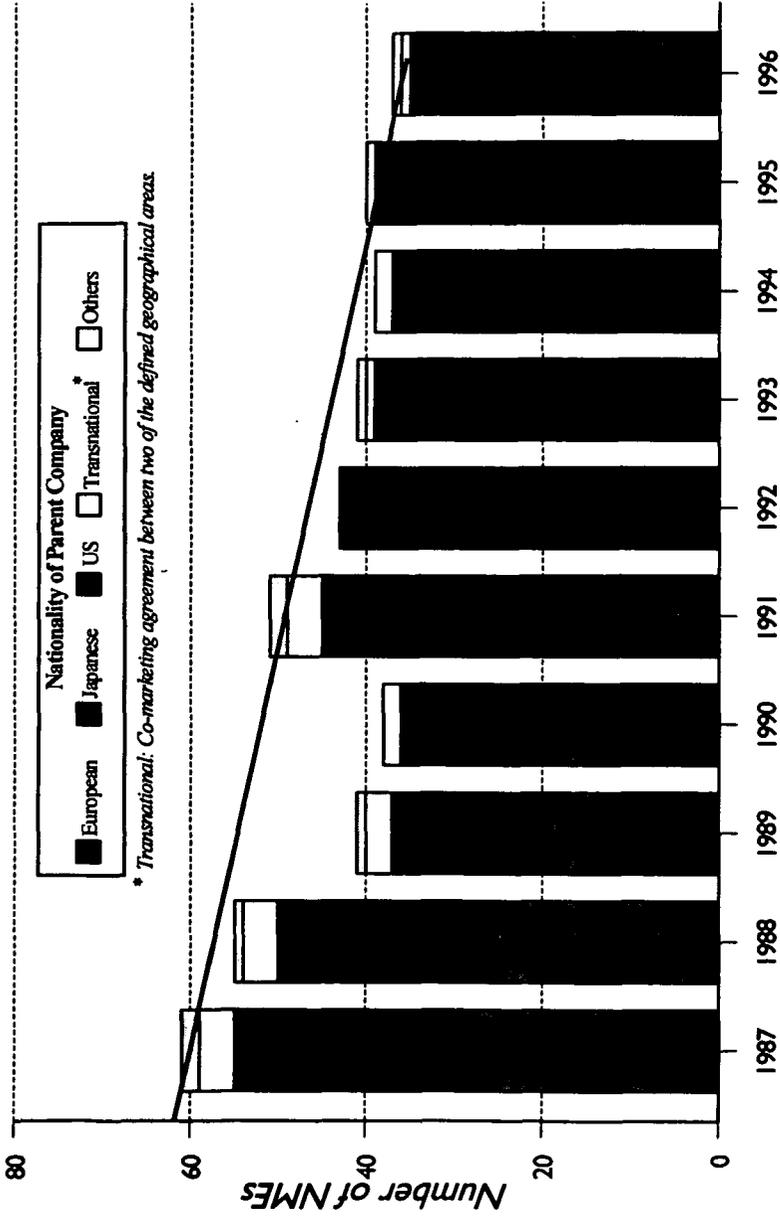
An examination of the various databases that identify and document the numerous products in the pipeline allows one to refute the critics of the

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4. Jurgen Drews, *The Impact of Cost Containment on Pharmaceutical R&D*, Centre for Medicines Research International Annual Lecture (1995).

5. Richard Sykes, *The Pharmaceutical Industry in the New Millennium: Capturing the Scientific Promise*, Centre for Medicines Research International Annual Lecture (1997).

**Figure 2**  
**New Molecular Entities First Launched Onto the World Market 1987-1996**



\* Transnational: Co-marketing agreement between two of the defined geographical areas.

**Year of First World Marketing**  
 Source: The Pharmaceutical R & D Compendium: CMR International/Scip Publication 1997



pharmaceutical industry who would like to imply that there is a concentration of resources and investment in a limited number of therapeutic areas. Since 1980, major advances have occurred in (1) cardiovascular therapy: ACE inhibitors and lipid lowering agents; (2) nervous system drugs: SSRI antidepressants, anti-migraine treatments, and major improvements in anaesthetics and anti-epileptics; (3) anti-cancer drugs: new products that significantly improve the chances of survival in several types of cancer and anti-emetics diminishing the problems of nausea and vomiting in chemotherapy; (4) anti-infective drugs: including drugs to combat HIV infection in AIDS, other anti-virals, and new antibiotics with greater effectiveness in treating difficult or resistant bacteria; (5) gastro-intestinal drugs: protein pump inhibitors, systemic anti-fungals, and drugs to avert the rejection of transplanted organs; and (6) the first important drugs from biotechnology and genetic engineering: erythropoietins, TPA, human growth hormones, colony stimulating factors, monoclonal antibodies, and others.

Several studies have endeavored to assess the innovative value of new products introduced into the world market but have failed in their methodology by limiting the assessment of innovation to chemical structure and clinical value. In order to appropriately describe the novelty of such medicines, one needs to take into account not only chemical structure, which perhaps is of least importance, but also the pharmacological mode of action, whether the medicine introduces a new therapeutic concept, its clinical value, whether it has an improved safety profile, and its socioeconomic benefit. Surrogate markers, such as whether the product is internationalized (on the major world markets including the United States, Europe, and Japan) and its sales value, might also be considered when examining innovative value. While the global pharmaceutical industry has continued to demonstrate innovative capacity as the pressure of cost containment has taken hold in the pharmaceutical and health care sectors, future innovations will depend on the pharmaceutical industry's success in continuing to meet the profit challenge. As noted earlier, high levels of R&D expenditure cannot continue without an adequate return on R&D investment. Pressure to continue to reduce costs will place disciplines on R&D that might reduce the scope for drug innovations; but it will be innovative medicines that provide the biggest boost to pharmaceutical companies in their attempts to generate sufficient revenue for R&D and profits. The first two challenges for the global pharmaceutical industry—the profit and innovation challenges—are interdependent in that one cannot be successfully handled unless both are.

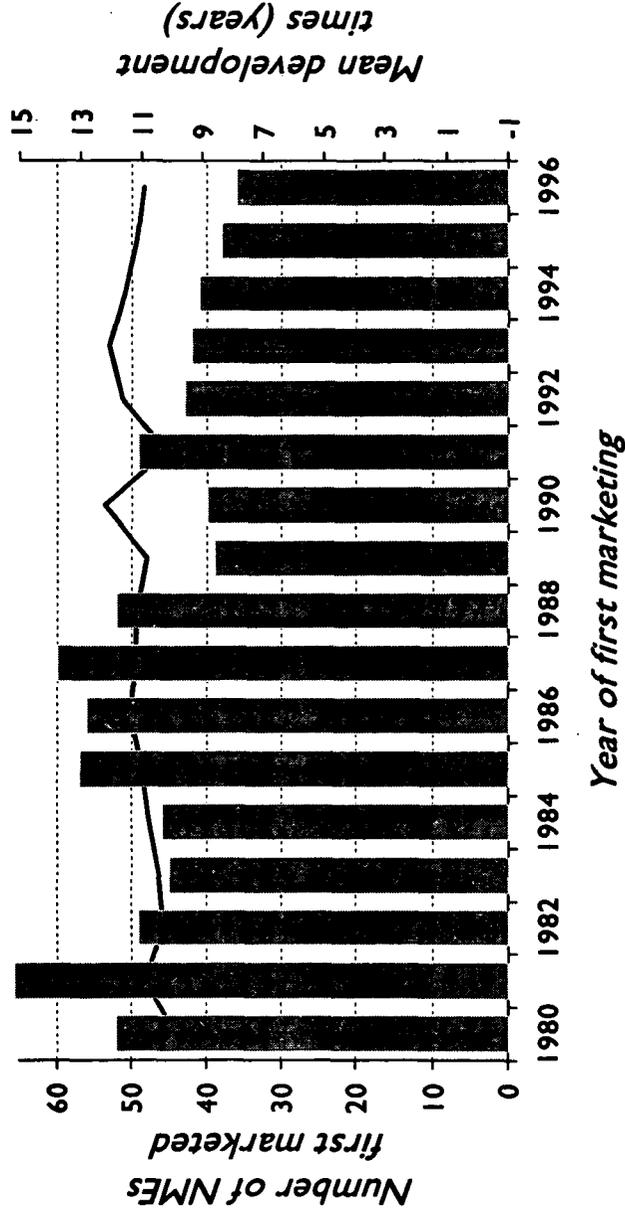
### III. THE EFFICIENCY CHALLENGE

The third challenge to the global pharmaceutical industry is to bring new medicines more quickly and efficiently to the marketplace for the benefit of society. CMR International's database of marketed medicines allows drug development time, defined as time from synthesis to the first marketing of the drug, to be examined over the past thirty years. In the early 1960s, development time was approximately two to three years [Figure 3]. By the early 1990s, development time had extended to approximately twelve years. However, over the past decade, development time has remained remarkably constant at between ten and twelve years, with some evidence that this has now started to decrease. There is widespread sentiment in the pharmaceutical industry that a ten to twelve year development time is too long and has to be shortened. Industry's response to this challenge is to set its target at around six to eight years, with an average of three years for the pre-clinical phase and an additional four years for clinical development of the drug.

In order to effectively reduce drug development times, pharmaceutical companies are looking at ways to reengineer the drug development process. Critical to reducing drug development time is the establishment of a benchmarking program to determine where time is lost and how the process can be speeded up and made more efficient. CMR International has established an on-going major benchmarking exercise that currently has the support of forty leading pharmaceutical companies, including seventeen out of the top twenty in the world. As demonstrated in Figures 4 and 5, this program has allowed the identification of "macro" benchmarks such as: first synthesis, first administration to man, first dose to patients for target indication, first dose in the first pivotal safety and efficacy trial, submission of first drug registration dossier, first launch in first market, and the subsequent launches into the top ten major markets for pharmaceutical products.

In addition, CMR International has defined "micro" benchmarks for the clinical development period. As seen in Figure 6, these include: protocol initiation to protocol approval, first patient to last patient enrolled, first dose to first patient to last patient last visit, last patient to database lock, and from database lock to approved report. These data are now being collected on a yearly basis, and the baseline data for over 300 new chemical entities investigated and 350 clinical studies conducted during the period 1994-95 have allowed for the establishment of a valuable database. Data will continue to be

**Figure 3**  
**Number of NMEs Introduced Onto a 20 Country Market 1980-96**  
**and**  
**Their Mean Development Time**



Source: *The Pharmaceutical R & D Compendium: CMR International/Scrip Publication 1997*

**Figure 4**

# Macro study : Major milestones

Discovery	Preclinical development	Clinical development	Application for first market	International launch programme
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Synthesis    First GLP tox dose    First human dose    First submission    First core market submission

Screened    Last day GLP tox    *Patient decision*    First approval    Last core market launch

*Preclinical decision*    *Human decision*    First patient dose    First launch

*Launch decision*

First dose first pivotal trial

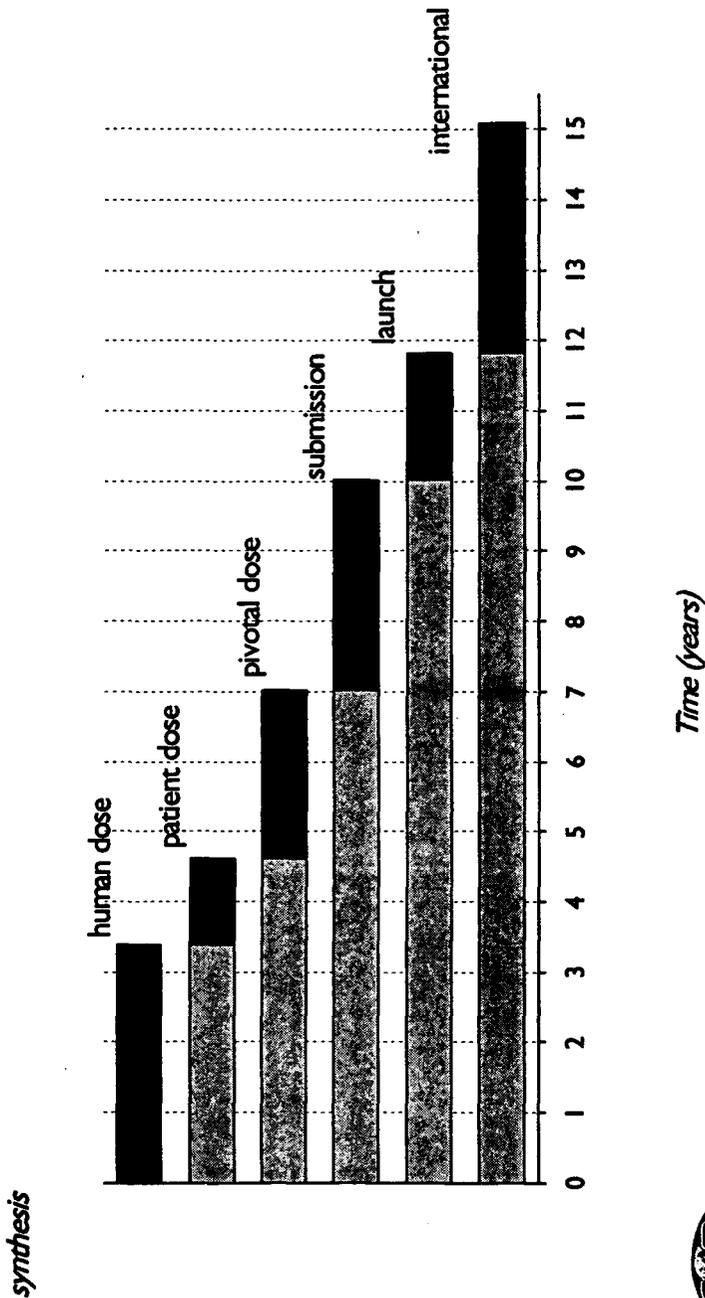
Last visit/last pivotal trial



Source: *The Pharmaceutical R & D Compendium: CMR International/Script Publication 1997*

# Figure 5

Hypothetical cycle time for NME in development in 1994/95 based on combination of mean values for completion of each interval in 1994/95



Source: *The Pharmaceutical R & D Compendium: CMR International/Script Publication 1997*

Figure 6

# Micro-benchmarking for Clinical Development



*Identify and define common benchmarks*

Source: *The Pharmaceutical R & D Compendium: CMC International/Scrip Publication 1997*



collected on a yearly basis and will permit the critical analysis of drug development times. This will allow pharmaceutical companies to share successful practices and the subsequent improvements in their time-lines. An example of such a time line is shown in Figure 7.

Nearly fifty years ago, Joseph Schumpeter stated that innovation has two components: the generation of novelty and the maintenance of novelty. The first component is achieved by discovery, dependent on the most intelligent and creative use of science. The second part of innovation is achieved by development and is based on process knowledge, logistics, and organization.<sup>6</sup> The challenge of bringing new medicines to market more quickly and efficiently will depend on the global pharmaceutical industry's success in improving the product development process through better knowledge of the process, more efficient logistics, and organization. Macro and micro benchmarks, such as those developed by CMR International, demonstrate that the development process can be reorganized to enhance efficiency. Schumpeter's two part definition of innovation also suggests that the efficiency challenge directly connects with the innovation challenge facing the global pharmaceutical industry. In addition, efficiency serves pharmaceutical companies well as they attempt to meet the profit challenge in the era of cost containment. Again, the challenges facing the global pharmaceutical industry are interdependent and must be approached as such by pharmaceutical companies.

#### IV. THE REGULATORY CHALLENGE

The final challenge to the global pharmaceutical industry is for governments to ensure an efficient and rapid review of new drug applications to allow innovative medicines access to the major markets. The introduction of regulatory requirements by the major governments of the world to ensure appropriate quality, safety, and efficacy of new medicines undoubtedly had a significant impact on overall drug development times by creating the need for a regulatory review process.

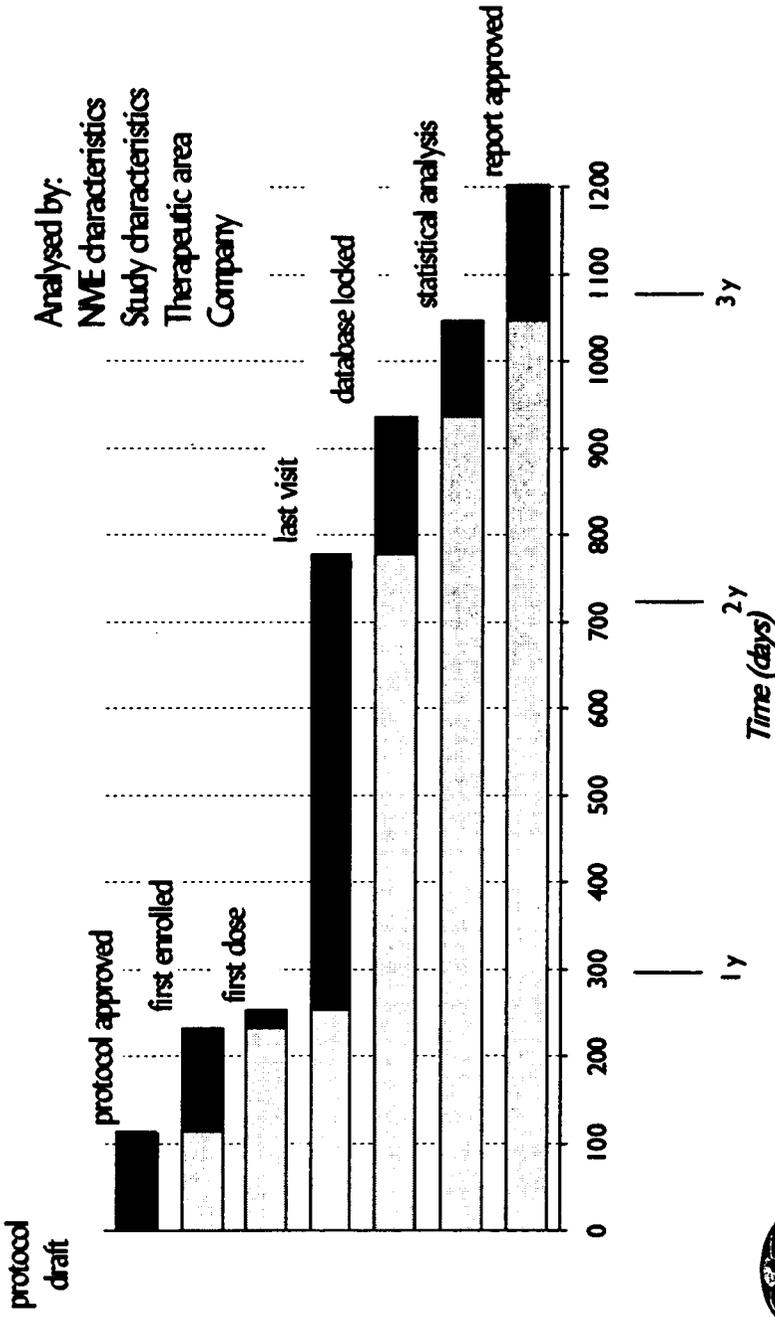
In the 1960s and 1970s, the regulatory review process for new drugs usually took only a few months. The development of increasingly complex and demanding regulatory procedures significantly lengthened the review process

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6. 1 JOSEPH A. SCHUMPETER, BUSINESS CYCLES 87-192 (1939).

**Figure 7**

# Time between key clinical milestones



Source: *The Pharmaceutical R & D Compendium: CMR International/Script Publication 1997*

so that in some countries the process could take three to four years. Given the absence of any centralized regulatory review process internationally, pharmaceutical companies were facing longer and longer regulatory review processes in all major pharmaceutical markets. As demonstrated by Figure 8, in the past decade, the data indicates that, in general, regulatory review times in different countries have decreased; but the median review time in nine major countries still remains between one and two and a half years.

To achieve the objective of a six month review period, two strategies are essential: (1) intergovernmental efforts at pharmaceutical regulatory harmonization through the International Conference of Harmonization (ICH) should be continued; and (2) partnerships between global pharmaceutical companies and national regulatory authorities should be formed to identify ways to streamline the review process without sacrificing necessary regulatory oversight. A recent initiative along the lines of industry-government collaboration is the identification of key milestones in the regulatory review processes of different countries, as shown in Figure 9, and the examination of the targets set by government authorities and the problems experienced in meeting the targets.<sup>7</sup> This type of collaborative study of the regulatory review process can help produce "good regulatory practices" to parallel "good laboratory practices" in the industry. Further, this approach can be used in many different countries, thus contributing to the goal of regulatory harmonization. Reengineering the drug review process to meet the regulatory challenge will also need to involve improving transparency, setting clear performance targets, assuring a consistent quality review, and reducing the information burdens the regulatory process places on pharmaceutical companies. The successful implementation of these ideas will require an improved dialogue between governments through mechanisms like the ICH and between regulatory authorities and the pharmaceutical companies.

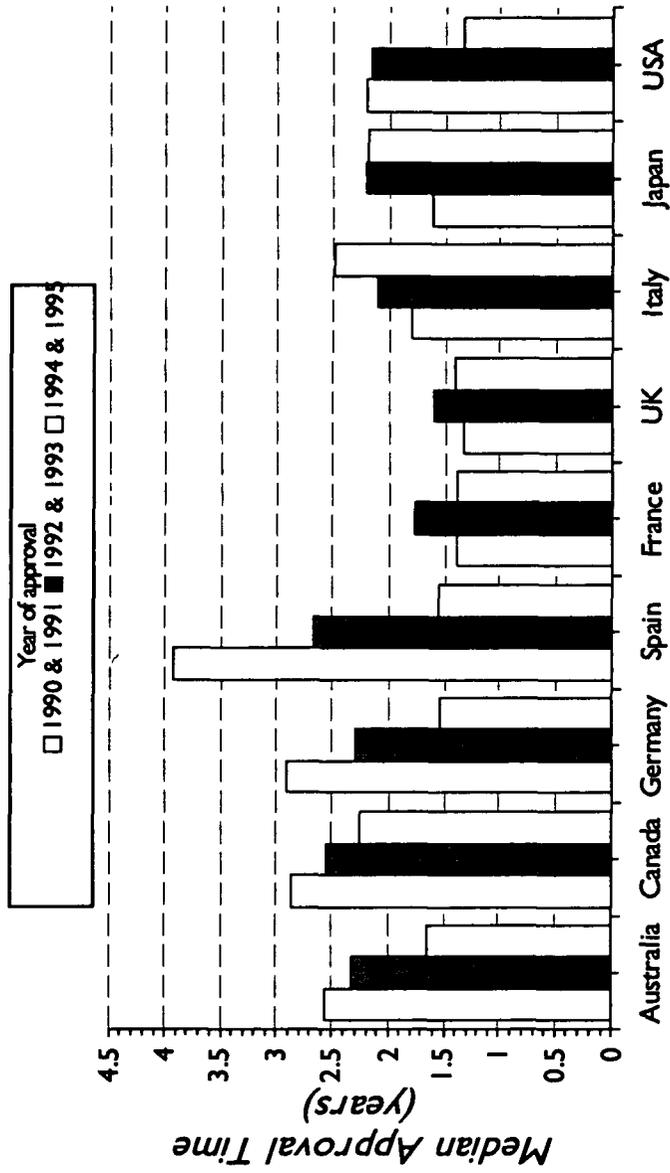
The interdependence of the challenges facing the global pharmaceutical industry is also apparent when considering the regulatory challenge. A successful reengineering of the regulatory review processes in major pharmaceutical markets will help companies deal with the pressure of cost containment, remove regulatory drag on innovation, and support getting drugs to market more efficiently.

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7. See generally CENTRE FOR MEDICINES RESEARCH INTERNATIONAL, IMPROVING THE REGULATORY REVIEW PROCESS: ASSESSING PERFORMANCE AND SETTING TARGETS, 1997 CMR INTERNATIONAL WORKSHOP (J.A.N. McAuslane & S.R. Walker eds., 1997).

**Figure 8**

**Median Regulatory Approval Times in Nine Countries (1990-1995)**



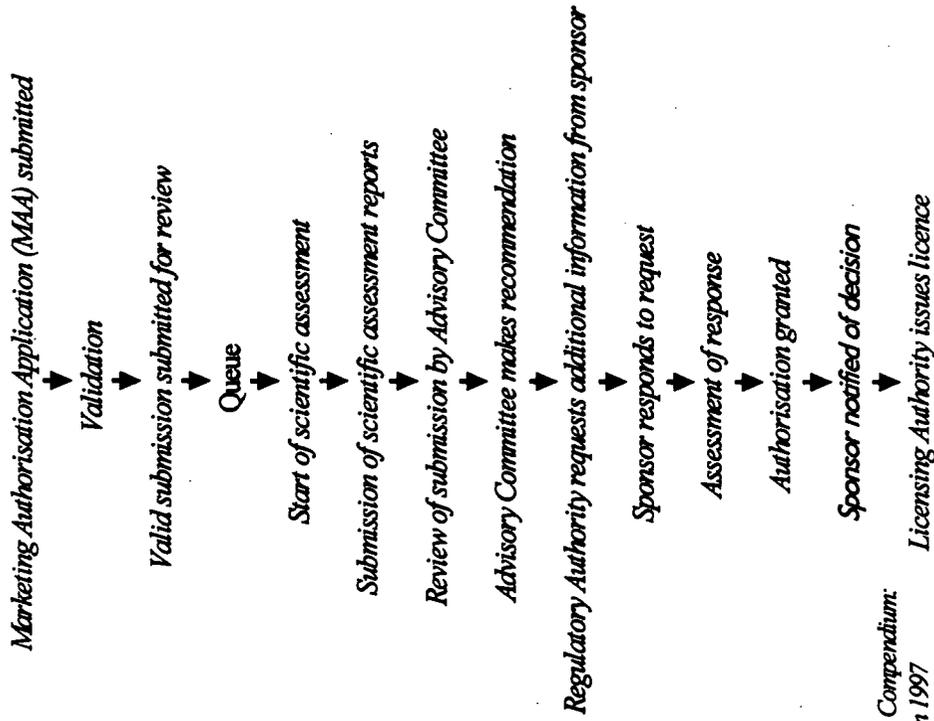
*Regulatory Authority*



Source: *The Pharmaceutical R & D Compendium: CRI International/Script Publication 1997*

**Figure 9**

# Generic regulatory review process



**Key Milestones**  
**Which are applicable?**  
**Which are recorded?**



Source: *The Pharmaceutical R & D Compendium*  
CMR International/Scip Publication 1997

### CONCLUSION

As we approach the new millennium facing many serious global challenges to public health and health care systems, the global pharmaceutical industry—as the main engine in the search for medicines to deal with infectious and chronic diseases—will play a central role in shaping responses to global health challenges. The four main challenges confronting the global pharmaceutical industry today—profit, innovation, efficiency, and regulatory challenges—are important, not only individually, but also as an interdependent set of challenges that must be addressed comprehensively. It is my experience that the global pharmaceutical industry is taking decisive steps to approach the challenges comprehensively, although much remains to be done. While my focus has been on the global pharmaceutical industry, it is important to remember that this industry does not alone bear responsibility for resolving the serious public health and health care problems present in many countries. Success by the global pharmaceutical industry in remaining profitable, enhancing innovation, improving efficiency, and helping regulatory reform is a necessary, but not sufficient, response to the health concerns facing humanity in the global era.

