

**Institute for Alternative Futures**  
**Foresight Seminars on Health and Innovation**

**SUMMARY**

FORESIGHT SEMINAR ON RESEARCH AND DEVELOPMENT  
IN THE GLOBAL PHARMACEUTICAL ECONOMY.

April 11, 1983

**ABSTRACT**

The pronounced globalization of the pharmaceutical industry has several implications for the United States. The U.S. is the biggest single-country pharmaceutical market in the world. Ten of the top 20 pharmaceutical manufacturers worldwide are U.S. companies. Yet there is reason for concern about the relative position of the U.S. in the global pharmaceutical economy.

One concern arises from increasing costs in research and development; this has encouraged companies to shift increasing shares of their R&D efforts overseas for a variety of reasons, including cost reductions. Not only does this affect research productivity in the U.S., it also influences what drugs reach the domestic market. As research moves abroad, foreign markets become more important and companies adopt strategies to take advantage of differences in international markets. One strategy is to develop drugs abroad first, where lower research costs minimize the impact of market failures, and then to introduce these drugs in the U.S. if they have proven profitable. Evidence that this occurs can be found in the drug lag, when drugs become available overseas months or years before they reach the U.S. Further evidence appears in the reduction of investigational new drugs (INDs) originating in the U.S. An increasing proportion of INDs are being filed on new chemical entities (NCEs) that originate abroad and are acquired by U.S. firms for the U.S. market. Smaller U.S. firms in particular are becoming dependent on the results of foreign research efforts. Thus, globalization of the pharmaceutical industry is causing changes in where drugs are developed and in how those drugs reach the U.S. market.

As globalization of the pharmaceutical industry takes place, it becomes more important for companies to be sensitive to conditions abroad. Economic factors force companies to seek international markets where there are very different needs. Because U.S. companies have historically depended on the large domestic market for sales, they may be at a relative disadvantage compared with foreign firms, which have developed a more international perspective.

Among the geographic areas, developing countries may offer a great potential growth market for pharmaceuticals. But the needs of these countries and pharmaceutical companies must be reconciled. There have been conflicts over marketing practices, patent protection and essential drug lists. This has worked against the interests both of developing countries, which need the health and economic benefits of drug development, and the pharmaceutical industry, which needs larger markets.

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### **BACKGROUND**

The influence of the global pharmaceutical economy is increasingly important to an understanding of policy issues, which affect pharmaceutical R & D in the U.S. The April 11 seminar presented three speakers capable of describing the global influences in the pharmaceutical industry. First, Tamara Erickson, Manager of the Pharmaceutical Unit of Arthur D. Little, Inc., described the pharmaceutical industry worldwide along with important trends. Next, William Wardell, M.D., Ph.D., Director of the Center for the Study of Drug Development at the University of Rochester, related the global influences to trends within the U.S. Then the final speaker, Robert Stein, LL.B., an attorney who works with international health and environment issues, discussed both real and potential relationships between the pharmaceutical industry and developing countries.

#### **Tamara Erickson**

The size and growth of the world pharmaceutical economy can be characterized along two important dimensions of the industry: geographic markets and therapeutic categories. The U.S. is the largest single country market with 17% of total industry sales; Japan is second with 14%. Western Europe comprises 33% of the market, with the remaining 36% distributed throughout the rest of the world.

Ms. Erickson presented growth forecasts for 1981-1986 for these four major geographic divisions: Western Europe, the U.S., Japan and the rest of the world.

Allowing for a 6% inflation rate in the U.S. pharmaceutical industry, the growth forecast for the U.S. pharmaceutical market is 12%, a rate slightly above that experienced during the past five years. Growth in the other markets is projected to be even higher than in the United States, with the rest of the world category expected to have the fastest growth of the four regions described.

These geographic markets also differ in their demands for pharmaceuticals. For example, in developing countries, anti-infective products account for 17% of the sales while more sophisticated cardiovascular products account for only 13%. In the U.S., on the other hand, anti-infectives only account for 15% of sales while cardiovascular products equal 18% of total pharmaceutical sales. The geographic differences in market demand is an important factor that shapes R&D decisions in the pharmaceutical industry.

A profile of the pharmaceutical industry shows that half of the top 20 pharmaceutical companies in the world in 1981 were U.S. companies.

The proportion of pharmaceutical sales in relation to the total corporate sales provides one indication of the emotional and financial commitment of a company to pharmaceuticals.

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The general orientation of a company and the character of its diversified businesses are also a good indication of the company's strengths. Companies fall into three broad categories:

1. Basic chemical companies that generally maintain strong synthesizing skills and are comfortable with the manufacturing elements of the pharmaceutical industry.
2. Consumer-oriented companies whose strength is often in marketing; and
3. Those participating broadly in the health care industry; often the focus of these firms is on technology.

The pharmaceutical industry is becoming increasingly international. Many of the leading companies have 38-40% of their sales in Europe; 25-32% in North America; 10-12% in Latin America; 9-15% in Asia and 5-6% distributed throughout the world. Japanese pharmaceutical companies were among the least internationally diverse in 1981, but are beginning to enter some of the markets in which they have previously not participated.

Of the top 20 companies, the average pharmaceutical related R & D expenditure in 1981 was \$130 million. This figure represents approximately 8-10% of the companies' pharmaceutical sales. R & D dollars are buying increasingly less; the cost of developing a single successful new product in the U.S. market is between \$70-75 million. According to figures from the Pharmaceutical Manufacturers Association, there has been a shift in the amount of U.S. founded R & D taking place abroad from 7% in 1963 to 18% in 1979. There is no indication that this trend will either slow down or reverse in the future. Two major factors have influenced this shift: 1) the cost of developing and marketing products in the U.S. is becoming increasingly more expensive; and, 2) because the costs are increasing, companies prefer to test products in foreign countries initially to develop a sense of certainty regarding the attractiveness of the products before bringing them to the U.S.--resulting in the phenomenon entitled "drug lag".

#### **William Wardell, M.D., Ph.D.**

There are three basic forces that shape the internationalization of R & D. The primary force is economic--specifically, reimbursement policies. The second force is scientific opportunities and the system of disseminating knowledge in the particular location. The third is a combination of local factors and conditions such as regulatory efforts toward harmonization. The Benelux agreement, the EEC's Committee on Proprietary medicinal products, the EFTA, and the Nordic group are all formal attempts at harmonization, but not all have been successful so far. Regulations are becoming harmonized, however, through de facto channels such as improved communications, etc.

Industry has contributed to harmonization through its desire to have international NDAs. This trend has been accelerated by the need for more licensing throughout the world. Especially for a foreign company, the topic of licensing raises many questions such as:

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where should a new drug first be introduced? Should the same company introduce the drug in every country? In what language should the research data be stored? Responses to these questions are rapidly leading to the acceptance of Western standards and concepts throughout the world.

The U.S. does not maintain the comfortable leadership position it once held in pharmaceuticals. In the mid 1970's there was a 50% decrease in the number of new chemical entities (NCEs) entering human testing from the entire U.S. pharmaceutical industry. This decrease was in addition to a 60% drop that occurred between 1961 and 1963. Conversely, the percentage of NCEs first studied by U.S. firms in humans' abroad rose from less than 10% through the late 1960s to 40% in the mid-1970s. Since that time the percentage has fluctuated. Furthermore, the number of new molecules licensed and acquired from abroad each year remained constant from the early 1960's to the late 1970's. so that the proportion of the total that are self—originated NCEs has fallen from 80% to 68%.

There are important trends in the flow of licensed compounds from abroad into small, medium and large U.S. firms. In 1979, licensed compounds made up 50% of the research portfolios of small firms, but only 12% of that of the large firms. Consider this in the light of the fact that there is a substantial difference in the success rates of self-originated and acquired new molecules: the success rate for U.S. companies' self—originated NCEs arriving at the stage of IND filing and then NDA approval is about 10%, while for acquired NCEs the success rate is three times as high -- 30%. (This difference is due in part to the fact that products are usually acquired after their efficacy has been proven elsewhere). Applying these differences in success rate to the existing differences, the proportion of licensed compounds, if we can predict that by the late 1980s, small firms will depend on acquired compounds for 80% of their new drug approvals, and taking all U.S. firms together, 60% of their NDAs will be on acquired compounds. The origins of these acquired compounds reveal another trend: Europe and the United States account for a declining proportion of acquired compounds, while Japan accounts for an increasing percentage. This trend has occurred in part because European companies are bringing their compounds to the U.S. market themselves, and because U.S. companies are not licensing from one another as much as in the past. It is interesting to note, however, that in 1981, only seven of the twenty-three new therapeutic drugs approved in the United States were of U.S. origin.

#### **Robert Stein, L.L.B.**

Developing countries are growing faster than other regions and they are probably the largest untapped markets for pharmaceuticals. There is a mutual interest in developing these markets that, according to Stein, must be recognized by development agencies, the pharmaceutical industry and Third World governments. There are a number of concerns involved including: marketing codes, essential drug lists, and patent rights.

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From the point of view of the Third World, the problems are seen as rapacious marketing practices on the part of companies, dumping of unsafe or unnecessary drugs and developing local industries. These problems need a cooperative approach to mediate the different interests. An example is the essential drug lists developed by the World Health Organization. The list does not imply that no other drugs are useful, but says that in a given situation, these drugs are most essential to health in developing countries. The list should be regarded as guidance rather than mandatory policy and one country that has considered making the list exclusive, Bangladesh, has postponed that decision. At the same time, the pharmaceutical industry should be sensitive to the needs of developing countries as expressed by the WHO list. One positive example is the development of oral dehydration salts, which are very inexpensive, but are effective against the leading cause of death in the Third World--dehydration from diarrheal diseases.

Despite the tremendous need, spending for research activities of major public health importance in developing countries was only \$50—60 million per year in the public sector. Another \$22 million was spent on research on parasitic diseases in private industry in 1979, but this is still not a large amount of money relative to the problems. According to a study conducted by the World Bank in the late 1970's, the per capita health budget in developing countries in the public sector ranged from less than \$1.00 to \$15.00. In the private sector, figures for pharmaceutical research on a per capita basis are somewhat higher. However, there needs to be more research on public health needs before the market for more sophisticated drugs can grow.

Foreign pharmaceutical firms appear to have spent a larger percentage of their research budgets for tropical disease research. This may reflect their historic recognition that the world is their market, not just the home country. However, in the United States, steps have been taken which can help with problems that exist in the area of pharmaceutical R & D for the treatment of third world diseases. Regulatory and legislative action may alter the economic trends of the past. New NDA regulations provide for the acceptance of clinical data from other countries and this could enhance the development of drug therapies for these areas. Passage of the Orphan Drug Act by the U.S. Congress was intended to encourage research on diseases which affect a small number of people. However, the language of the bill would also allow research into diseases which affect only a few people in the United States, but many people worldwide. This means there is a possible 73% tax credit for up to five years for clinical studies on orphan drugs as well as a possible \$4 million in grant money for the research.

Another factor which may make R & D for third world countries more viable is patent extensions. There are serious problems with countries not protecting patents. This may keep Research and Development from taking place and it is a problem that needs a cooperative solution. International health organizations are involved as they are buying drugs that are manufactured under pirated patents. They have a short-term interest in buying the cheapest products available, but in the long run this may make fewer drugs available if it inhibits research and development. There may be other ways to make drugs available at a lower cost in the future, including: 1) bulk purchasing; 2) agreements to

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restrict advertising to reduce costs; and 3) determining the health priorities of bilateral and multilateral agencies. He predicts that if pharmaceuticals are going to be able to do the job they were intended to do in developing countries and in other parts of the world, these changes, as well as others, must take place.

According to Stein, one way to begin mediating between poor countries (such as Bangladesh or Sri Lanka), and large pharmaceutical companies, is to ask serious questions about the primary interests of both groups. What do the countries want to do for their people with the resources they have? What are the pharmaceutical companies' interests with respect to how they wish to approach sales? Often, when countries must choose priorities, companies, as well as multilateral and bilateral lending agencies, can assist them. This can lead to the establishment of acceptance patterns.

### **QUESTIONS AND DISCUSSION**

The question was raised whether Japan's national support for biotechnology has particular implications for the international pharmaceutical trade. Erickson responded that biotechnology in Japan has focused primarily on antibiotics and other fermentation based products. She predicted the advent of a broader range of products coming from Japan based on their government support of fermentation techniques in conjunction with biotechnology.

Another question was raised as to the possible acceptance of limited antitrust immunity in the pharmaceutical industry due to the rising costs of R & D. Dr. Wardell responded that such a practice may not be appropriate because in a sense the basic research effort, supported by government and carried out at universities, results in knowledge that can be shared, while development attracts single companies who do not wish to relinquish their competitive advantages by working with others. A possible opportunity for collaboration may be in the area of very large scale drug studies, on the scale, for example, of the multiple risk factor intervention trial.

Tamara Erickson was asked whether or not she foresaw any trend toward large companies moving some of the research in the development of new drugs into developing countries through their subsidiaries. Erickson does not foresee such a trend for a variety of reasons. The infrastructure in developing countries is so weak that providing credible documentation for re-entry into the U.S. market would involve a large up-front expenditure in those countries. Also there are occasionally racial differences in reactions to particular drugs. Hence, it is not advantageous to conduct research in one market only. There was a question whether strict regulatory policy resulted in differences in health patterns. Wardell said that health patterns are difficult to compare internationally to prove cause and effect relationships. According to Stein, the distribution system of health services within countries is clearly linked with health patterns. Countries with more advanced or effective distribution systems are generally healthier than those with less advanced systems.

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**CLOSING STATEMENTS**

**Robert Stein**

There are ways to overcome patent problems with products for developing countries. For example companies could try imparting compounds and then permitting the final assembly within the country. Harmonization is going to succeed more quickly at the front end of tests (i.e. developing testing guidelines, good lab practices, etc.) but some discretion must be left to the regulatory agency in each country. It is clearly in the interest of companies and countries to make a concerted effort to make the system work better.

**Tamara Erickson**

The pharmaceutical industry will continue to be more international. There has been, and will continue to be, significant progress in managing that international activity. Many companies are setting up research facilities in important international markets and forming linkages with other companies who understand local requirements in certain key countries. It will be increasingly important to determine how foreign companies compete and what types of opportunities exist internationally.

**William Wardell**

Science and regulation of the pharmaceutical industry will not be the major constraints on improving global pharmaceutical R & D in the future. Economics, particularly the nature of the health care reimbursement systems (including drug payment methods) in place in just a few major countries, will be the main factor that determines how easily scientific advances will be translated into useable new medicines.