Orphans and Incentives: Developing Technology to Address Emerging Infections

Polly F. Harrison and Joshua Lederberg, Editors; Forum on Emerging Infections, Institute of Medicine

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Workshop Report

Forum on Emerging Infections

Polly F. Harrison and Joshua Lederberg, Editors

Division of Health Sciences Policy
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Preface

THE FORUM

The Forum on Emerging Infections was created in response to a request from the Centers for Disease Control and Prevention (CDC) and the National Institute of Allergy and Infectious Diseases (NIAID). Its goal is to provide structured opportunities for regular, open, nonadversarial communication among representatives from academia, industry, professional and interest groups, and government.[1] Their interest—and the Forum's mandate—is to examine and discuss scientific and policy dilemmas of shared interest that are specifically related to research on and prevention, detection, and management of emerging infections.[2] In accomplishing this task, the Forum can foster exchange of information and ideas, identify areas in need of greater attention, clarify policy issues by enhancing knowledge and identifying points of agreement, and inform decision makers about science and policy issues. We underscore here that the Forum seeks to illuminate issues rather than resolve them directly; it does not provide advice or recommendations on any policy pending before any agency or organization. Its strength rests on its diversity of membership and the commitment of individual members to attend on a recurrent basis.

The linchpin of the Forum's work is a series of workshops focused on linked topics. The first, on which this document reports, was organized around the broad theme of public-/private-sector collaboration. The topic for the second workshop is antimicrobial resistance, surveillance, and response. The third workshop will examine the implications of health care restructuring for addressing emerging and re-emerging infectious diseases.

THE TOPIC

In today's world, infectious diseases remain a leading cause of prolonged illness, premature mortality, and soaring health costs. According to the World Health Organization (WHO), of 52 million deaths of all ages in 1995, approximately one-third were attributable to infectious diseases. Worldwide, acute respiratory tract disease and pneumonia accounted for 4.4 million deaths, diarrheal disease and tuberculosis for 3.1 million each, malaria for 2.1 million, hepatitis B for 1.2 million, and measles and HIV/AIDS for 1.1 million each. In the United States in that year, infectious diseases constituted the third leading cause of death, just behind heart disease and cancer, with mortality mounting over time, owing to HIV/AIDS, to pneumonia, especially in the elderly, and to septicemia, with drug resistance playing an ever-increasing role in each of these disease categories. Infectious diseases also account for over 25 percent of visits to health care providers yearly, as well as an ever greater percentage of hospital admissions. The underlying premise of the Forum is that the mortality and morbidity deriving from infectious diseases are, all things equal, untimely and unnecessary.

The reasons for the global emergence over the past two decades of new diseases and of old diseases with new faces, are various and complex; so are their ramifications. Both were explored in the 1992 Institute of Medicine report, *Emerging Infections: Microbial Threats to Health in the United States*. That report laid a basis for the strategic plan developed in 1994 by the CDC in partnership with others concerned with those threats: federal agencies; state and local health departments; academic institutions; professional societies; international organizations; and experts in public health, infectious diseases, clinical practice, and medical microbiology.[3] The CDC strategy, in turn, was the catalyst for the deliberations of the Committee on International Science, Engineering, and Technology (CISET) of the National Science and Technology Council, convened to review and make strategic recommendations concerning the U.S. role in detection, reporting, and response to outbreaks of new and reemerging infections. [4] And, for years, NIAID has been calling attention to "orphan" diseases, for example malaria, and trying to stimulate both industry and government R&D investment.

Both the CDC and CISET strategies pointed to the utterly critical function of cross-sectoral partnerships in responding to emerging diseases. CISET's recommendation is explicit:

> The U.S. Government and private sector should work together to establish a better investment environment for the production of urgently needed medical products. This can be accomplished by combining the resources of national and international government institutions with the technical expertise in the U.S. pharmaceutical industry and in other sectors of the private health care industry.

The rationale for this collaboration is straightforward, as recently argued before the U.S. Congress:

> No biotechnology or pharmaceutical company can afford to support, at the level needed, the kind of work carried out by thousands of laboratory and clinical investigators in our nation's universities, medical schools, and independent research institutes. In turn, only the for-profit biopharmaceutical industry can translate into products the fundamental insights gained from such publicly supported investments.[5]

The CISET recommendation goes to the heart of the Forum's mandate and was therefore chosen as the topic of its first workshop, the objective of which was to shed light on the primary constraints in that investment environment and on what might serve to ease them. The workshop title, "Orphans and Incentives," refers to the fact that those constraints have left an undefined group of "urgently needed medical products" in an orphaned condition which demands special attention.

THE REPORT AND ITS ORGANIZATION

We ask the reader to remember, first, that any single workshop is necessarily incomplete and, second, that its proceedings can only report on what was said. Thus, the report does not pretend to be an exhaustive exploration of its subject matter. It is organized as a topic-by-topic synthesis of exchanges during the workshop; its purpose is to highlight lessons from relevant experience, delineate a range of pivotal issues and the problems they present, and put on the table some simplified ideas about possible responses. An appendix to the document contains a compendium of mechanisms and strategies attempted over the past couple of decades to promote research and the development of health technologies that constitute particular market challenges. The original purpose of the compendium was to provide food for thought for the Forum members about past models and available options; it was incorporated into this report as a similar resource for the reader.

Although speakers are not identified by name in the text, the reader should understand that the material presented reflects the views and opinions of those participating in the workshop, not the deliberations of a formally constituted Institute of Medicine (IOM) study committee. All members of the Forum have reviewed the document and responded that they thought the report accurately reflected what happened at the workshop. All information reported in the text emerged in the workshop itself; where presenters and discussants referred to a specific document or a key allusion needed more explication to be intelligible to the reader, an endnote is provided.

ACKNOWLEDGMENTS

On behalf of the Forum and the IOM, we wish to express our warmest appreciation to the individuals and organizations who gave valuable time to

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NOTES

1. Representatives of federal agencies serve in an ex officio capacity.

2. Emerging infectious diseases are diseases of infectious origin whose incidence in humans has increased within the past two decades or threatens to increase in the near future (Institute of Medicine. *Emerging Infections: Microbial Threats to Health in the United States* . J Lederberg, RE Shope, SC Oaks Jr, eds. Washington, D.C.: National Academy Press, 1992.)

3. U.S. Department of Health and Human Services, Public Health Service. *Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States.* Atlanta: Centers for Disease Control and Prevention, 1994.

4. National Science and Technology Council (NSTC). *Report of the NSTC Committee on International Science, Engineering, and Technology (CISET), Working Group on Emerging and Re-Emerging Infectious Diseases* . Washington, D.C.: Office of the President, 1995.

5. L Rosenberg, cited in: B Metheny, Testimony from industry, academia, and professional societies supports status quo in resource allocation at National Institutes of Health, Washington Fax Life Science, May 8, 1997.

Contents

Summary

This workshop of the Institute of Medicine's Forum on Emerging Infections set out to learn from experience what has been done and what is needed for the public and private sectors to collaborate effectively and productively for the health of the public. The emphasis was on cooperation in those product areas where returns from the market might be perceived as too small or too complicated by other factors to compete in industrial portfolios with other demands for investment. Quintessential examples of such products are vaccines, and in some instances therapies, for the diseases of children, for malaria, and for HIV/AIDS. Each of these offers lessons for attempts to deal systematically with emerging infectious diseases. While there are differences between the public health requirements of developing countries and industrialized countries, the growth of the middle class in the former and the vulnerability of the latter to diseases once thought to reside permanently "offshore" are doing much to narrow those differences.

The primary study case for the workshop was the Children's Vaccine Initiative (CVI), formally established in 1991 as the first comprehensive effort to yoke public- and private-sector scientific advances to a global public health priority through purposive intersectoral collaboration. The lessons learned from the CVI were integrated at the workshop with other experience from disease-focused efforts, notably malaria and HIV/AIDS. The purpose of this report was to integrate that learning and the tasks it suggests as points of reference for further action.

LESSONS

The lessons learned fall into four sets of messages around: what makes intersectoral collaboration "real," the notion of the product "life cycle," the implications of divergent sectoral mandates and notions of risk, and the roles of advocacy and public education (see Table 1).

TABLE 1 Lessons Learned

Authentic Intersectoral Collaboration

- Implementing collaboration between the public and private sectors that goes beyond rhetoric is difficult.
- Beginning partnerships early and sustaining them with regular interactions at several institutional levels is at the core of making cross-sectoral collaboration real and useful.
- A critical—and informative—test of real collaboration is the sharing of information not customarily shared, for example, product leads in the pipeline, pricing rationales, early data from trials, and ongoing priority-setting processes.

The Product "Life Cycle"

- Pharmaceutical research and development are most usefully addressed as a total process that expresses the push-pull dynamic between supply and demand, and offers opportunities for incentives all along the pathway from bench to market.
- The market for publicly needed products is not self-evident, so that clear, consistent pictures of public-sector needs, priorities, and policies, as well as potential market sizes and characteristics are essential.

Divergent Sectoral Mandates and Notions of Risk

- In the private sector the bottom line is defined by timely financial return. The public sector also needs to take account of competing priorities for resource allocation in terms of public health results.
- The cost of pharmaceutical R&D is sizable but its dimensions are poorly understood.
- For both sectors, R&D investment decisions derive from interactions among costs, time, and predictability; how those compare across different investment options; and the relative risks they produce.
- Public- and private-sector views of risk differ but since both sectors confront it, pooling at least some risks is likely to motivate taking them.

Roles of Advocacy and Public Education

- The high value of advocacy and public education in promoting individual disease priorities and catalyzing public awareness is increasingly well appreciated.
- However, the public sector and important elements of the nonprofit sector underuse their powers for advocacy for generic public health needs such as vaccines, as well as for needs seen as most important outside national borders.

These lessons, taken together, signal needs for: (1) more information, (2) more predictability; and (3) more sharing of costs and risks, if the requirements for products for emerging infectious diseases are to be satisfied. Looked at systematically across the product cycle, these sort into more specific categories where incentives might be developed to bolster the competitiveness of such public health products in industrial portfolios. Table 2 on the next two pages lays out these categories, highlighting actions expected to be especially critical for advancing the infectious disease enterprise as a whole.

Because a fresh look at the market for these products is believed to be primary for awakening commercial interest, the demand side is presented as leading the

cycle. The emphasis here is on interventions that can make markets more attractive by expanding knowledge, limiting demand uncertainties, and generating appealing economies of scale, with most dramatic effect likely when these are conceptualized early in the R&D cycle. Emphasis on the supply side is focused on solidifying the financial resource base, sharing information, balancing out investment risks, and reducing the time and costs of clinical research.

The sense of the workshop was that this was a reasonable framework for action, with the next logical steps being decisions about who might stimulate action most quickly and effectively in each area, perhaps beginning with those requiring building consensus and possible legislative modifications. Since microbes are agile and fast, it might be said that there is little time to lose.

TABLE 2 Incentives for Increasing Pharmaceutical Research and Development for Priority Infectious Diseases

What Is Needed	Demand Side	Supply Side: Basic Research	Supply Side: Clinical Phases
More information	**Market identification** • epidemiologic/burden of disease data • ongoing, accessible, integrated, comprehensive surveillance data on disease trends and resistance patterns **Priority setting** • well articulated, consensus-based public health agendas • clear portrayals of specific disease priorities • product characterization	**Disease-specific bioinformation system** • research data from universities, research councils, biotechnology companies on product leads for possible development by industry	**Development of surrogate endpoints** • generic categories of endpoints for use with a range of infectious diseases • alternatives to correlates of protection for vaccines for which clinical trials difficult or impossible
More predictability	**Market assessment** • early forecasting of demand based on epidemiologic criteria from surveys, demographic analysis • segmentation by size, ability to pay, disease profile • cost-effectiveness analysis	**International regulatory harmonization/reinforcement of intellectual property rights**	**Restricted distribution/product labeling** • systematic exploration of tension between need to conserve usable life of antimicrobials while conserving market appeal for R&D investment

More cost- and risk-sharing	**Market creation** • procurement guarantees via: high-volume bulk orders, extended contracts, product "bundling" subsidies for poorest countries • revolving funds for national and/or regional purchasing • ODA for health infrastructure and education, drug logistics **Multi-tiered pricing** • careful articulation of rationales to re-start legislative dialogue	**Patent extension** • exploration of extension of patents for expired compounds with potential utility in new antimicrobials • explicit inclusion of antibiotics under Patent Term Restoration Act **Stabilization of funding** • examination of R&D implications of ODA decreases, annual volatility **Financial support** to universities and biotechnology companies for taking promising leads to proof-of-principle **Venture fund** for early-stage development of product leads	**Orphan drug legislation** • exploration of applications of OD law in developing products for emerging infections, especially niche products, with primary market outside U.S.A. **Accelerated regulatory approval** • accelerated enrollment in trials • aggregation of efficacy data from multiple sources • continuing the progress in predictability and efficiency in regulatory oversight processes **Building CRO capability** in developing countries to reduce costs and enhance infrastructure for clinical trials **Financial subsidy** for phase II/III trials, with payback on success

NOTE: ODA = Official Development Assistance; R&D = research and development; OD = Orphan Drug; and CRO = Contract Research Organization.

We want to acknowledge the importance to this table of the list, presented at the workshop by the representative from the World Bank, of suggestions from a survey of pharmaceutical company executives on how to promote health product development for low-income countries. The tabular material presented here is a broader synthesis that draws on the whole range of workshop presentations, including discussions of public-sector needs and priorities; industry perspectives on needs; lessons learned from the Children's Vaccine Initiative and other models; and legal and regulatory issues involved in development of drugs and vaccines for emerging infections. That there is so much concordance about which areas merit attention, as well as the kind of attention they require, is impressive.

Introduction

BACKGROUND

In the first months of its existence, the members of the Forum on Emerging Infections worked to shape clusters of issues that they considered fundamental to the Forum's rationale and therefore central to its work. At the top of the list were questions about what technologies would be needed to address emerging infections, who would determine and articulate those needs, how the necessary technologies would be produced and by whom, what would motivate and support that production, and in what ways all these matters might be affected by situations of urgency.

Consensus has evolved over the past few years that emerging infectious diseases will require a range of responses, many unanticipated, that will surpass the capacities of either the public health sector or the private industrial sector working alone. Yet, at the same time that collaboration between those two sectors is seen as a *sine qua non*, their mandates are seen as quite divergent. And, although there is also consensus that special energy must be dedicated to somehow bridging those mandates, there is little unanimity about what sorts of bridges might work best.

For both sectors, economics is a fundamental matter, even though constituencies and demands for accountability differ. The public sector must obtain adequate budgetary allocations for its work, allocations that depend at least in part on the constituencies it can marshal in support of that work; its incentives derive from getting the public health agenda right and responding satisfactorily to the appropriate populations. And, while profitability is not part of its mandate, the public sector is increasingly required to be attentive to costs. The private industrial sector must obtain adequate financial rewards for its constituencies, that is, those who invest in its ventures. Mobilization of that investment depends importantly on profits from the markets for its products. If there are disincentives either to those markets or to satisfactory levels of reward, offsetting incentives are required. Although these do not have to be purely economic, they must ultimately have some sort of economic effect.

A large economic challenge to market demand is presented by the inability of significant numbers of potential customers for a given product to pay its full cost; this in turn constrains the ability of private investors in research and development to recover their investment and make a profit. Returns to investment and profit-making are also affected by other costs, for instance, responding to regulatory requirements and protecting against liability or compensating claims, particularly when any of these are extraordinarily unpredictable.

All these costs are taken into account when private developers craft portfolio strategies and scrutinize investment alternatives. Furthermore, and very importantly, companies invariably assess costs, risks, and benefits relative to one another. Take, for instance, the case of vaccines for malaria and AIDS, two very complex infectious disease categories that entail exceptionally high levels of R&D risk. A company must compare potential payoff from investment in a malaria vaccine for a large market of low-income consumers with a correspondingly low per-dose profit), with potential payoff from investment in an AIDS vaccine (for a smaller market of consumers who either have relatively high incomes or may be able to rely on health insurance or public-sector subsidy for drug purchase). An increasingly germane issue has to do with the costs consumers and providers are able and willing to cover and, in the era of managed care, what technological investments will generate the biggest savings to those who provide health services.

A crucial subset of concern has to do with industry response to health problems that may be critical but are of such relatively small scale that the market potential they represent is either not apparent or is unappealing in terms of prospective R&D investment. This lack of appeal may prevail even when the benefits from solutions to the health problems in question go beyond prevention and cure of diseases in individuals, such that they also have considerable benefits for the health of the public and, by extension, the well-being of the society as a whole. From this perspective, such technologies can be thought of as "social products," material goods that express important societal values but are nevertheless inefficiently or inadequately represented by market forces. Of these, a significant group—vaccines, contraceptives, pharmaceuticals for managing drug addiction, and diagnostics and therapies for at least some infectious diseases, including sexually transmitted diseases—raises special challenges to decisions about R&D investment. The challenges are primarily economic but in some cases, cultural and sociopolitical factors become weighty and even determining.[1]

The social products problem becomes acute when the technology at issue responds primarily to requirements of the less developed countries, as has been the case with many infectious diseases. In 1992, R&D claimed just 3.4 percent of the world's total expenditure on health. Of the almost $56 billion invested in health research in 1992, approximately 95 percent was invested in health problems that primarily affect the industrialized world; just 5 percent was devoted to the health needs of developing regions. Combined research and development spending on the three leading disease conditions in developing nations—pneumonia, diarrheal disease, and tuberculosis, diseases accounting for almost

one-fifth of the entire global burden of disease—totalled $133 million, or 0.2 percent of the world's entire health R&D spending.[2] Historical, socioeconomic, and geographical distances may once have served to justify that extreme imbalance; they make little sense now, as pressures from epidemiological and demographic mobility grow and multiply.

THE WORKSHOP

These core concerns led the Forum members to ask more specific questions about the present and future challenges of infectious diseases, questions then used to organize this workshop. They were:

- What is the public health agenda for emerging and reemerging infections in those areas where specific responses will be required from industry, and what products are needed?
- Of those, which product areas are already a focus of significant industry research and development (R&D) efforts and which product areas are, in effect, "orphans," unlikely to be developmental priorities because their market future is somehow unappealing, especially if they present complex and costly technical challenges?
- What approaches have been used to assure the development of products that are not profit makers but are nonetheless essential to the health of some significant population, that is, "social products"? Which of these approaches might reward further exploration as a way to deal specifically with the issue of emerging infectious diseases?

Because the ramifications of these questions are so varied and extensive, the decision was made to take case material as a point of departure for analysis and discussion. The primary case chosen was the Children's Vaccine Initiative (CVI), with case material on the Malaria Vaccine Development Board and International AIDS Vaccine Initiative added to expand the basis for discussion. Conceptualized in the late 1980s, launched subsequent to the World Summit for Children in late 1990, and a continuing focus of international effort since, the CVI has accumulated enough history to provide many lessons about strategies, tactics, and issues, all potentially valuable for thinking about how to attain a reasonable level of preparedness for infectious diseases as they emerge and re-emerge at some level of compelling concern.

Workshop Summary

THE CHILDREN'S VACCINE INITIATIVE*

A Brief History

The CVI was established to marshal the quantum advances in the science of vaccinology toward new pediatric vaccines with qualities expected to significantly enhance immunization coverage for all the world's children, with some (but not exclusive) emphasis placed on children of the developing nations.[3] The issue was not that no new vaccines were being produced. On the contrary, beginning in the mid-1980s, after decades of modest growth mostly driven by each year's births, the vaccine market had entered a phase of dramatic expansion, and commercial vaccine manufacturers and biotechnology firms were busy developing innovative vaccine products.[4] The target market was the industrialized world. Products exclusively for a developing-world market were viewed as unlikely to offer adequate returns under then-current market arrangements and were therefore commercially unappealing.

The CVI's mission was to alter the prevailing R&D orientation and to supply new products and models to those developing-country markets. The founders of the CVI—the Rockefeller Foundation, United Nations Children's Fund (UNICEF), United Nations Development Program (UNDP), World Bank, and World Health Organization (WHO)—realized that accomplishment of that mission would be impossible without collaboration between the public sector and industry. Although the public sector in the United States had historically conducted most of the basic research leading to development of new or improved vaccines, product-oriented R&D was undertaken almost exclusively by vaccine manufacturers and development-stage firms, with only a handful of major commercial vaccine manufacturers having the capacity to scale up and manufacture vaccines on the large scale required for global application.[5] The public sector had tended to look at vaccines as a separate series of scientific problems, or as product development problems, or as delivery problems, rather than as an "end-to-end," integrated

* This section documents the presentations and discussions pertaining to Element 2 of the workshop agenda, "A Learning Case: The Children's Vaccine Initiative."

process unfolding over a considerable period of time. The CVI would need to adopt a more comprehensive approach to the total cycle and to a range of approaches for reducing its duration in some kind of partnership with industry.

The implications of this prospective cross-sectoral strategy would prove to be far greater than anticipated, rooted as they were in distinct sectoral cultures, divergent incentive structures, and mutual perceptions that augured poorly for authentic collaboration. The public sector had historically denigrated the profit motive, correspondingly mistrusted all industrial motivation, and did not fully understand the real costs and effort involved in developing a vaccine. The private sector viewed the public sector as motivated by ideology, not economically realistic, and unpredictable, and feared the vagaries of politics and bureaucracy as essentially threatening to what it saw as its legitimate interests. A core strategy for the CVI was, necessarily, to build trust between these two traditional adversaries. Its leadership needed, therefore, to be concerned with educating both sectors, demonstrating that doing well in terms of profitability and doing good on a humanitarian level were compatible, and somehow modifying the structure of incentives for the vaccine industry—domestic and international—to produce those products defined by the public sector as priorities. The fact that, at the outset, the CVI suffered from a surfeit of bureaucracy and turf struggles would, for a while, constrain its ability to meet its own objectives.

Defining and Implementing Cross-Sectoral Collaboration

The CVI began with only a vague notion of what would be implied by "public-/private-sector collaboration," especially in a product area with so little apparent economic appeal and with so little hard cash as evidence of public-sector commitment to the Initiative. "Funds available" to the CVI Secretariat leveled off between 1993 and 1995 at about $2 to $3 million a year, including funds earmarked by donors for particular tasks. These levels are seen as insufficient for critical new activities such as communications and work with industry and, even though overall income looks as if it may grow, donor specifications will continue to limit program flexibility.

The initial CVI meetings, with government representatives at the table and industry representatives around the sides of the room, accurately reflected the CVI worldview in its early days. Another early cultural artifact was the limited presence of industry overall, confined as it was to a relatively few individuals with whom there had been some kind of historical relationship. And, because they were not suppliers of vaccine to UNICEF or to the Pan American Health Organization (PAHO), U.S. vaccine producers were not adequately included in these first encounters.

These phenomena no longer prevail. The range of industries involved with the CVI has expanded and industry's representatives are brought into dialogues sooner in a more consultative fashion, although some feel still not soon enough; and the cross-functional, cross-organizational team approach has slowly proved more

effective. The reasons for these shifts should be instructive, proceeding as they did from heightened sensitivity on the public-sector side, greater mutual understanding of sectoral motives and functioning, the CVI's growing ability to define critical areas of coincident interest, and practical implementation mechanisms.

Defining, Creating, and Stabilizing the Market

Situation Analysis

There is consensus that a most useful and in many ways groundbreaking CVI undertaking was the contracting out, to professional private-sector management consultants, of the task of analyzing the economics of the vaccine industry, thereby providing a fresh evidence base for policy determinations.[6] The first situation analysis by Mercer Management Consulting calculated the size of the world vaccine market in 1993, then estimated at around $2 billion annually, and revalued it at almost $3 billion and growing rapidly; the basic pediatric vaccines accounted for one-third of that market. The report also discussed the dynamics of the world vaccine market and examined the role of large-scale purchasing by donors.[7] Overall, the study provided both sectors with a common understanding of economic realities, helped the public sector feel informed and therefore able to work with industry as an equal partner, effected change in public-sector strategies, and modified industry perceptions of market potential. To date, three Mercer analyses (1994, 1995, and 1997) have been conducted, the latest of which addresses the key factors of pricing and supply as related to product life cycles.

Market Segmentation

Another CVI innovation that has enhanced private-sector views of the world vaccine market was segmentation of that market by country groupings according to ability to pay. The result has been that UNICEF no longer donates vaccine to any nation requesting it but now targets donations and shapes its strategy to fit "bands" of countries, each band speaking with a distinct "market voice" (see Figure 1). The first two bands (A and B), comprising the poorest and smallest countries or "the CVI market," receives frank donations or highly preferential prices. The intervening mechanism is that UNICEF purchases, or subsidizes purchases, of vaccines on behalf of those countries. The third and fourth bands (C and D) contain the larger countries with higher per capita incomes, that are being strongly encouraged toward self-sufficiency either through direct procurement or local production, and who can also afford a higher price point, although they are not always pleased to do so. The fifth band (E) consists of the industrialized Western countries, the primary market for international suppliers and for newer vaccines.

FIGURE 1. A global targeting strategy for sustainable vaccine supply, as defined by Bands A-D, and market segmentation and tiered vaccine prices according to the primary market of international suppliers, direct procurement, local production and the UNICEF market. SOURCE: A. Batson, WHO Global Program for Vaccines and Immunization. Reprinted with permission.

The decision to segment derived partly from concerns about funding sustainability and the need to target limited funds to the neediest countries.[8] The premise was that industry would only provide a lowest-tier price if that price were limited to countries where market forces had failed. A reconstituted customer list would also serve as an incentive to many more countries to begin buying vaccines, in turn providing greater incentives to manufacturers, particularly U.S. manufacturers, to reassess the developing economy market.

The policy has evoked controversy and its ultimate success will be highly dependent on two lead factors: (1) the value assigned by putative purchasers to vaccines, especially to newer and more costly formulations, and on the prices those purchasers are able to negotiate with industry; and (2) agency commitment to helping countries find ways to purchase their own vaccines. Nevertheless, the segmentation approach provided a platform for such negotiation, between UNICEF and industry for the neediest countries, and between industry and countries in the higher-income bands.

Centralized Procurement

The Mercer study concluded that, in the case of vaccines, high-volume public-sector procurement does "move the market," that is, it influences manufacturers'

behavior and thus can help or hinder achievement of public-sector programmatic goals. The fact that UNICEF purchases 40 percent of the supply of traditional vaccines produced by 10–12 core suppliers, and roughly 20 percent of the total global supply of these vaccines, has been crucial to expanding demand for vaccine doses over the past eight years.[9] For manufacturers with large excess production capacity, the increases in plant utilization generated by guaranteed high-volume purchases by UNICEF and PAHO have permitted them to use that capacity, thereby driving down per-dose production costs; this is believed to have been the most important economy of scale in terms of making sales to UNICEF attractive even at relatively low prices.[10] In addition, the learning curve associated with greater cumulative volume is understood to be very steep and recognition of manufacturing process economies comes with corresponding speed; thus, production experience with large volumes serves to drive costs down still further and more quickly.

UNICEF also modified its customary commodity-driven approach to evaluating potential source manufacturers and incorporated three more requirements into its tender procedures: information about the overall product portfolio a bidding company could offer to meet the needs of the developing country market, those products a company might offer that responded to UNICEF/WHO priorities in the tender period, and the company's R&D pipeline.

In addition, because the CVI, WHO, and UNICEF are interested in access to newer vaccines—Hib conjugates, hepatitis B, and, eventually, pneumococcal conjugate vaccines—they have worked together to find ways to make procurement processes more flexible and to explore with industry ways to create value other than price—for example, "bundling" vaccine orders, using supply contracts, and extending contracts beyond the typical duration of two years.[11] These approaches and other efforts at true partnership have motivated some vaccine companies to donate vaccines, provide cash grants to special immunization programs and disease surveillance, lower prices, make selected new products available in some preferential fashion, and furnish R&D pipeline information for assessment by WHO/UNICEF advisory groups.

Tiered Pricing

The backbone of public-sector access to new vaccines is a strong "tiered" pricing system in which the relative ability to finance vaccines is translated into different price levels for different countries. Some countries, including industrial country governments, pay a price for a given product that covers the full costs of production as well as the costs of overhead and R&D, and provides a reasonable return. Other countries, namely the poorest countries in bands A and B, are charged a price that covers the marginal cost of producing marginal volume for these markets, plus a small contribution to overheads. This price does not cover R&D, investment in new facilities, marketing expenses, or a number of other costs not associated with supplying this market. The middle, wealthier countries (bands

C and D) pay different prices covering production and varying levels of contribution to overheads and R&D. This strategy, which has been crucial in building up national immunization programs and expanding coverage worldwide, is entirely based on marginal volume with marginal costs and resulting marginal prices, and does not increase the price to the U.S. consumer. In fact, the concept was advanced that producing solely for the United States market may make U.S. manufacturers higher-cost producers.

However, confusion about the economics underlying cost allocation has resulted in criticism in the United States and, occasionally, other countries.[12] U.S. vaccine manufacturers have not bid on a UNICEF or PAHO tender since 1982, when the industry was criticized by members of the United States Congress for selling vaccines for use in developing countries at prices lower than those offered to U.S. public- or private-sector purchasers; a comparable criticism was levied in 1993.[13] Also during the period 1993 to 1995 in Congress, another battle was waged over differential pricing, this time related to large-scale vaccine purchases by the U.S. government at prices substantially lower than those listed in the private sector.[14]

Although tiered pricing can play such a powerful role in industry decisions to invest in vaccine research, development, and production, discussions of the subject have often generated more heat than light. The mechanism could conceivably play a role in connection with emerging infections—HIV/AIDS may prove to be the most immediate example—but the public sector has yet to frame a refined and thoughtful argument to take to the Congress for more reasoned, less stereotypic discussion than has been the case. The task cannot be done by industry alone, because its motives will inevitably be perceived as suspect, particularly when the topic is a "public good" with undertones of entitlement. Drug pricing tends to be a contentious issue in and of itself, so that the components of the arguments that will need to be made are subtle and complex, requiring good evidentiary material, meticulous analysis, and careful explication, perhaps, in connection with infectious diseases, by such entities as the concerned professional societies.[15]

Intellectual Property and Its Protection

Intellectual property protection has been used as a policy tool for many years within the United States to promote "the right amount of research and development in the country." The mechanism rewards inventive activity with the government's promise of a certain period of exclusivity in the marketplace in exchange for full public disclosure of the invention in question, at the end of which period the invention falls into the public domain.

In the pharmaceutical industry, owing to the lengthy time required to bring a product to the market, the period during which R&D investment can be recouped may become quite brief. To remain successful, a company must have products in its pipeline in all different phases of the "product life cycle." Mature products, approaching expiration of their patents and soon to face increased competition, are

then replaced in the marketplace with new products, whose exclusivity will refresh the company's stream of earnings. Substantial interruptions in this process may threaten a company's very existence and, in fact, explain much of the contemporary explosion in industry mergers. R&D investment risks become too high to reasonably assume without adequate patent protection which becomes, as a result, a major driver of industry economics and innovation.

Patent policy has also become central in U.S. foreign trade policy. The Trade-Related Intellectual Property Rights (TRIPS) Agreement, hammered out in the General Agreement on Tariffs and Trade (GATT) negotiation process and put into effect in the United States and Europe on January 1, 1996, set minimum standards for intellectual property protection around the world. It includes protection for pharmaceutical products, a 20-year patent period as a minimum standard, and an adequate judicial enforcement system. Developing countries were given until the year 2000 to adhere to the TRIPS standards; an "IPR-resistant" group, which includes India and Argentina, was given until 2005 to adopt product protection for pharmaceuticals.

A CVI-sponsored meeting in Brazil in 1995 explored the position previously held by many in the public sector that patent protection was an obstacle to vaccine production in developing countries. At a CVI-sponsored follow-up meeting in Bellagio, Italy, in February 1997, it became clear that protection of and respect for intellectual property are now seen as rational and defensible stimuli for further innovation, a position that has been adopted as a focal activity for the CVI and for the International AIDS Vaccine Initiative (see following discussion).

Technology Transfer

The CVI began at a time when the prevailing wisdom in the international health community was that local production would be an inherently less costly, more reliable, and more affordable way to ensure vaccine supply in the developing world. With limited exceptions, that premise seems to have failed the tests of time and careful economic analysis. Even though over 53 countries worldwide now produce one or more of the basic childhood vaccines, the quality, reliability, and real costs of those vaccines have proven problematic in a number of respects and CVI strategy has been revised accordingly. CVI and WHO have shifted to proposing that each facility do a fundamental review of its long-term viability and address the financial, managerial, regulatory, and policy implications of the upgrading needed to be a reliable, quality, affordable supplier of current and future vaccines. In that connection, participants in the February 1997 CVI/Rockefeller Foundation conference in Bellagio on "The Global Supply of New Vaccines" announced agreement that, to justify public confidence in the safety and effectiveness of vaccines produced in developing countries for national immunization programs, assurance of their quality would have to be independently overseen by well-functioning national control authorities. Such assurance will be

crucial to entering into the sorts of public- and private-sector partnerships that can permit access to new technologies, including new vaccines.

Individual Product Experiences

A More Heat-Stable Polio Vaccine

Many connected with the early Polio Eradication Initiative, including the WHO/EPI Technical Advisory Group, called for research on a more heat-stable polio vaccine, believing that it would be essential to the growing commitment to eradicate the disease worldwide. Despite lack of an industrialized market for such a product, some progressive members of the business community decided to take a risk within their own companies and attempt to prove that doing well and doing good could be stretched to include something as marginal to their customary market as a more heat-stable polio vaccine. As a consequence, industrial effort and investment were deployed and the project became something of a test case in intersectoral cooperation.

Over time, however, public-sector agreement on the need for an improved vaccine, already not unanimous, became still less so with changes in CVI leadership, resistance from operational levels, and new technical and epidemiological insights, some better-founded than others. Eventually, a decision was made to abort the project. Unfortunately, the private-sector partners were not involved in the relevant processes of consultation and decision. This was perceived as a major breach of trust, yet its ramifications for future intersectoral relationships were not appreciated by the public-sector decision makers, new to working with industry and not sensitive to its understandings of investment and risk.

This history was contrasted with that of the 1976 swine influenza vaccination program, when what has been called a disaster ensued as a consequence of an agenda that did not adapt to shifts in circumstance. [16] Despite disparities between many aspects of the two events, they send a similar message: the need for a scientific and technical consensus; an explicit decision in advance as to the market for a successful R&D effort; periodic review and reevaluation that is both broad and meaningful; and, throughout, close consultation between public- and private-sector collaborators. The swine flu affair taught an additional lesson of prospective relevance to emerging infections disease: Programs to prevent such diseases are essentially insurance policies, entailing some risks almost by definition, rather than subjects for punishment when anticipated dangers fail to materialize.

The Hepatitis B Vaccine

The case of the hepatitis B vaccine is somewhat different, yet lack of unanimity in some public-sector quarters remains an issue. The hepatitis B vaccine was developed in the United States for a market in the Western industrialized

nations that was viewed as small but potentially lucrative. The independent International Task Force on Hepatitis B made the argument to industry that this narrow market could be expanded profitably to a much larger market in the developing world if the vaccine were sold at a substantially lower price for use in immunization programs in those nations; the lower price would be offset by high-volume sales, in other words, through a tiered pricing system and subsidized bulk procurement. Driven partly by the Task Force's argument and partly by the entry into the market of competitive products, the initial price of $30 was subsequently progressively lowered to less than $1 per pediatric dose, and, in 1992, WHO recommended that the vaccine be introduced into national immunization programs, most urgently in hyperendemic areas.

That recommendation encountered resistance in some international agencies and developing countries, resistance rooted primarily in questions about cost, whether hepatitis B is properly considered a "childhood disease," the relative merits of the two principal vaccine formulations, and concerns about delivery capacity and sustainability. The resulting mixed messages to industry, always concerned about predictability, suggest the desirability of different public-sector approaches to product introduction in connection with the new acellular pertussis vaccine, haemophilus influenzae type b (Hib) conjugates, and the measles-mumps-rubella combination (MMR).[17]

OTHER MODELS*

The Malaria Vaccine Development Board

Malaria is not a formal focus of the CVI but is nonetheless highly relevant to a discussion of the CVI because of the disease burden it generates for children and because of the practical and theoretical challenges it shares with the Initiative. And, of course, malaria is most relevant to Forum concerns about the special challenges of addressing those emerging and reemerging infections that predominantly threaten the developing countries. Until very recently, malaria has been the quintessential example of a pharmaceutical "orphan," partly because of the challenges the disease and its vector posed to science, partly because there has not been a prevailing view that the disease threatened the industrialized world.

The recommendation that a Malaria Vaccine Development Board be established resulted from a workshop under the aegis of a small multisectoral committee at the IOM in 1996, charged with evaluating current international malaria R&D efforts and making recommendations for implementation by the U.S. government.[18] The committee concluded that even though research now indicates that it will be, in fact, technically possible to protect against malaria with

* This section documents the presentations and discussions pertaining to Element 3 of the workshop agenda, "Other Models and Mechanisms."

a vaccine, development of such a vaccine will be neither simple nor straightforward. The complex life cycle of the parasite will require combining multiple antigens, a novel delivery system, and the use of adjuvants to stimulate immune system response. There also may have to be two end-products: a vaccine that will provide short-term protection, primarily for the military and travelers' markets, and a vaccine that will modulate infection and reduce mortality in children in endemic areas, that is, the developing world.[19]

A related complication has to do with intellectual property rights. At one time, patents on malaria antigens served to stimulate research and development but, with time, they have become something of a problem. Pieces of what may be significant intellectual property are scattered around the globe. Some patents are held by Australian organizations and companies; some by Swiss, French, or U.S. companies; some by universities. There are also potentially important adjuvants that remain unlicensed and whose protection may be an issue. Aggregating all the intellectual property rights for a multicomponent, multi-antigen vaccine is a formidable dilemma that cries out for remediation.

There is also the market question. Despite the huge burden of disease produced by malaria—as many as 500 million cases a year and around 2 million deaths—the potential market for malaria vaccines has not been understood in a way that might stimulate continued investment. The fact that malaria is associated with large populations of the very poor, in regions where the delivery of health products is typically difficult, led industry to conclude that the market for a malaria vaccine would be primarily donor-dependent, with little representation from more affluent segments of developing country populations, with the limited exception of the military and travel markets. The combination of some or all of these factors, together with failure in earlier commercial development efforts, deeper understanding of the technical challenges involved, and an erratic pattern of support for public-sector malarial research, was what had led to attrition in the relatively few industrial and public-sector R&D efforts that had managed to get under way.[20]

The IOM committee's primary conclusions were that the dimensions of the problem demanded a commensurate commitment, and that the United States would have to take a leadership role in the search for a malaria vaccine. A secondary conclusion was that the tasks at hand—making the international case for support, attracting many more resources from all sectors worldwide, assembling the critical scatterings of intellectual property, performing a competent reassessment of developing world market realities—are necessarily multisectoral activities. The Malaria Vaccine Development Board is envisioned as a central organization that would focus communication among industry, the academic and military research communities, and public-sector donor and technical agencies, to get these tasks performed and stimulate the synergy lacking among what had become a very few parts.[21]

The International AIDS Vaccine Initiative (IAVI)

Like malaria, HIV/AIDS is not a formal focus of the CVI but is similarly relevant to a discussion of the Initiative. Both affect large populations, of which the majority are outside U.S. frontiers and very poor; both present daunting scientific challenges; and both must deal with failure of the market to stimulate the necessary levels of R&D investment. The IAVI and the notion of the Malaria Vaccine Development Board were included in the workshop discussion as possibly informative variations on the CVI approach to solving a "social product" problem.

The exploration that led to the establishment of the IAVI in 1996 began in 1993, when HIV vaccine research, stymied by technical difficulties, was at a nadir in comparison with the level of investment in HIV/AIDS therapies. Although the prospect of DNA vaccines has awakened greater interest in vaccinology in general, only a few companies have active programs in the area of HIV and only one HIV-DNA vaccine has progressed to human trials.[22] Furthermore, these programs focus almost exclusively on subtypes found in North America and Europe.

The purpose of the IAVI is to help accelerate development of preventive HIV vaccines appropriate for use where the epidemic is spreading most rapidly, that is, the developing world; to compensate for the fact that no agency has a mandate corresponding to that purpose; and to remedy the lack of international coordination, backed with adequate resources, to accomplish what is really a global objective. The Initiative has three overarching strategies: (1) advocacy for vaccine development; (2) a "push" strategy to support targeted research and development on parallel tracks; and (3) a "pull" strategy to create a more enabling environment for vaccine development. Its scientific emphasis is on gaps in existing efforts and on accelerating applied R&D. Its first-phase scientific objectives are to focus on development of HIV-DNA vaccines and expanded safety studies of live-attenuated HIV vaccines.

The IAVI's initial backing was provided by several foundations, UNAIDS, and the World Bank. That funding base is now being broadened to include new sources. A key element in IAVI's financial strategy is to try to persuade the Bank, which has already committed over $700 million in its response to the global AIDS epidemic, to establish a $100 million line of credit for each of the 10 most disease-burdened countries. The rationale is that this would, in effect, create a $1 billion market into which research costs could be amortized as an incentive to industrial investment. The general concept is to load the front end of the R&D process using public-sector funds to drive a directed research effort.

The IAVI has also begun to invest energy in intellectual property rights issues. As vaccine development has become more complex, every stage of the R&D process is now likely to be patented. The acquisition of multiple patents was critical to the development of the hepatitis B vaccine and, as indicated above, is expected to be critical in the development of a malaria vaccine. The IAVI will attempt to determine how it can use intellectual property rights as incentives for industry to work with the Initiative in developing and distributing an HIV vaccine. Liability will be another strategic area for the IAVI; the example was cited of

recent legislation in California which provides relief from certain elements of liability to manufacturers of vaccine in that state.

AN INDUSTRY PERSPECTIVE ON THE EMERGING INFECTIONS AGENDA*

Periodically, the Pharmaceutical Research and Manufacturers of America (PhRMA) surveys the pharmaceutical industry to ascertain amounts of clinical research in a given disease area. These surveys are published as part of a series entitled *New Medicines in Development*. The last such survey on infectious disease showed that, as of mid-1996, there were 125 products in testing for infectious diseases: 38 vaccines, 27 antibiotics, 25 antivirals, 14 antifungals, 18 "other biologics," and 3 immune enhancers, for diseases ranging from travelers' diarrhea to genital warts to typhoid fever (see Figure 1).[23] These totals do not include the new medicines in development for AIDS; according to a November 1996 PhRMA survey, there were 122 medicines in testing for that disease (see Figure 2). The 1996 survey showed a 33 percent increase over PhRMA's 1994 survey, reflecting greater industrial activity later in the anti-infectives pipeline but virtually no truly new compounds of the sort that will be needed to address growing problems of antimicrobial resistance.

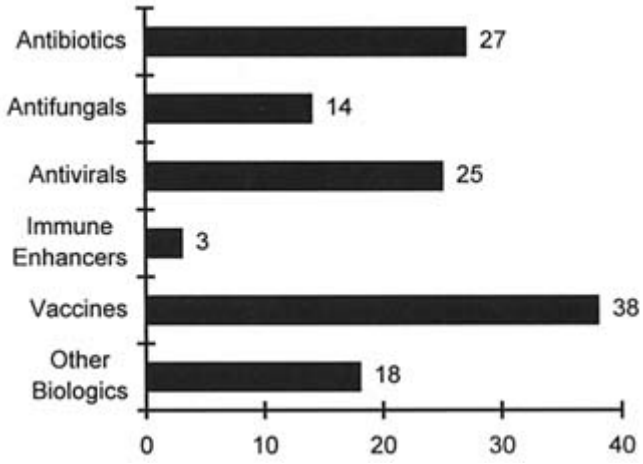

FIGURE 2. Number of medicines and vaccines in development for infectious diseases, 1996. SOURCE: J. Siegfried, Pharmaceutical Research and Manufacturers of America. Reprinted with permission.

* This section documents those portions of Element 1 of the workshop agenda that presented industry perspectives.

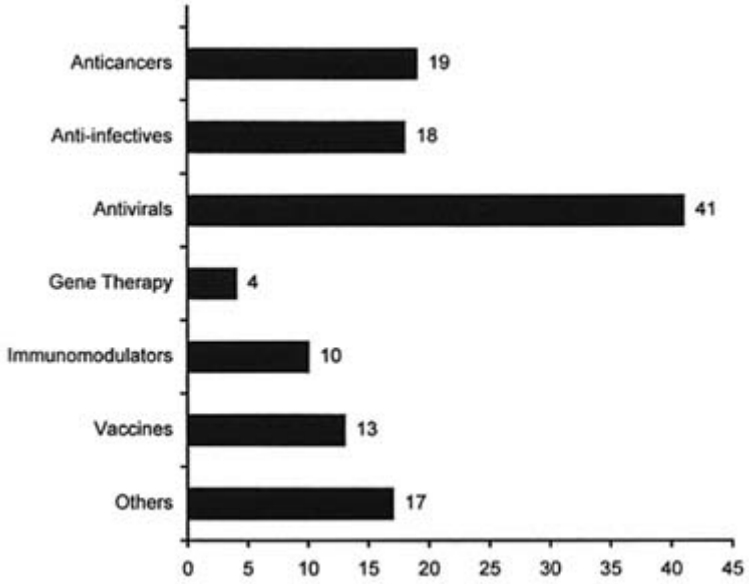

FIGURE 3. Number of AIDS medicines and vaccines in development, 1996. SOURCE: J. Siegfried, Pharmaceutical Research and Manufacturers of America. Reprinted with permission.

Although there is understandably some overlap of products, particularly for opportunistic infections occurring in AIDS sufferers and in the general population, the total of the two surveys places the number of clinical research projects currently in process for infectious disease at well over 200. In 1996, industry R&D expenditure on infectious disease of $2 billion was exceeded only by industry R&D expenditures in the categories of cardiovascular disease, cancer, and neurobiological disease.[24]

Many of these projects are not new anti-infectives but new dosage forms or new indications for established products. Still, modifications such as changes from multiple-dosing to once-a-day regimens, or from a poorly absorbed to a more readily absorbed product, may contribute to greater patient compliance and enhanced product usefulness. For example, several of the sexually transmitted diseases (STDs) are now treatable with a single dose of the appropriate anti-infective, and multiple-dose, long-term therapy for most urinary tract infections is now a thing of the past. Because R&D expense and time for development of a new indication or line extension may sometimes equal that of the original drug application, physicians face the dilemma of having to decide if and how to prescribe therapies that are unapproved, that is, off-label; this dilemma may be exacerbated by the fact that Food and Drug Administration (FDA) regulations do not presently permit pharmaceutical companies to disseminate scientific information concerning off-label uses to health care professionals.

If the public health agenda is to rapidly define and develop anti-infective agents for new and emerging infections, then the question is, how prepared is the pharmaceutical industry to accomplish such a task? One approach to an answer is to review the industry response to HIV/AIDS.

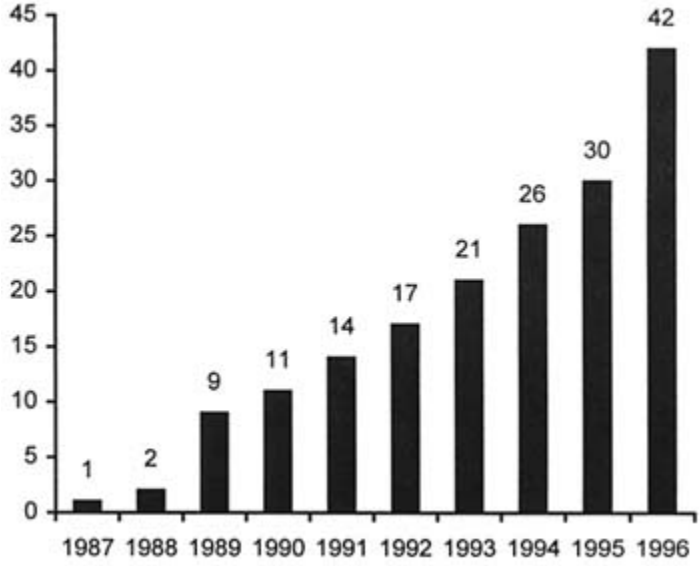

FIGURE 4. Number of approved AIDS and AIDS-related medicines, 1987–1996. SOURCE: J. Siegfried, Pharmaceutical Research and Manufacturers Association of America, annual survey: New Medicines in Development for AIDS (1996). Reproduced with permission.

Industry's Response to HIV/AIDS

The syndrome was first discovered in 1981. The etiologic agent was confirmed in 1983. The first diagnostic test was approved in 1984, the first antiretroviral in 1987. In the decade from 1987 to 1997, 42 medicines were approved for HIV/AIDS and its associated conditions. From an industry perspective, that is a remarkable achievement; from a societal, public health perspective, it is less than gratifying. Even though we now know how to prevent HIV, it still occurs in increasing numbers of individuals. Attempts to develop a preventive vaccine have been frustrating and the low efficacy of the vaccines developed so far raise large ethical and practical questions. And, although the success of a triple cocktail of a protease inhibitor plus two standard-entry antiretrovirals is much praised and offers some hope, there are still questions concerning when to start therapy, how long to continue it, the extent and duration of efficacy, and how to finance it.

The Emerging Infections Scenario and HIV/AIDS

The scenario for emerging infections is expected to be better for several reasons. First, the wealth of understanding that has come from HIV research, notably concerning the intricacies of the immune system, viral replication, and target sites of organism invasion, provides a large, specific foundation on which to build. Second, new technologies developed in response to HIV, for example, kinetic PCR assays and multiparameter flow cytometry, already lend themselves to better detection of current infectious diseases and will certainly be an asset for the future. Third, public awareness of the threat of emerging infections has grown, and movies, books, television, in fact all the media, continue to capitalize on this theme. Fourth, global surveillance for antimicrobial resistance and for emerging infectious disease is progressing. WHO's Division of Emerging and Other Communicable Diseases and Surveillance and Control has made "WHONET" software available to laboratories in its global network for the input of antibiotic resistance data, and PhRMA's contribution in June 1996 helped make possible the extension of WHONET to Africa; the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) is actively collaborating with WHO in this endeavor.

There are at least two significant lessons to be learned from HIV/AIDS that might be extrapolated to future emerging infections. One is the effectiveness of an activist community: ACT-UP, Treatment Action Group, Queer Nation, and other groups catalyzed public awareness and evoked response from the pharmaceutical industry, the FDA, and, on occasion, the Congress.

The other lesson is that cross-industry cooperation concerning a particular public health need is feasible. The Inter-Company Collaboration for AIDS Drug Development, a first-ever consortium, was established in April 1993 by 15 pharmaceutical companies who agreed to work together to facilitate early combination and comparative studies of antiviral agents and thereby accelerate development of drugs for treatment of HIV infection and AIDS. The heads of research and development in the 18 companies now members of the Collaboration share relevant preclinical and clinical data, expedite access to investigational drugs supplies, and develop standardized preclinical assays and procedures and other activities.[25] Cross-industry cooperation has also occurred in less direct fashion: The AIDS Clinical Trial Group established by NIAID serves as a nexus for government and private-industry collaboration on specific clinical research issues.

Finally, the flexible and innovative character of the FDA response to AIDS provides many ideas for the future. Special mechanisms such as expanded access and parallel tracking and inclusion of activists in formal advisory bodies are just two of those (see following discussion, Legal and Regulatory Issues).

Barriers

Many of the same issues that exist today as barriers to pharmaceutical development will remain in force, without special efforts to modify them. Pharmaceutical research is expensive: In 1996, estimates for the costs of developing a drug ranged from $359 to $500 million. Of every 5,000 projects that start the journey toward the pharmacy shelf, only one completes it and, of those that do, only one in five actually returns its R&D investment. These two factors alone force the product selection environment to be much more specific and to assume even greater weight in product areas—for example, pediatrics, orphan diseases, and oncology—that may lack sufficient population size to make commercial development attractive. Still, overall investment by the pharmaceutical industry in research and development is large: The proposed research budget for the pharmaceutical sector in 1997 is approximately $19 billion, 21.2 percent of its domestic sales and exports. By way of comparison, in other industrial sectors of the U.S. economy, average R&D investment as a percentage of sales is under 4 percent.

Another compelling factor is time. The standard figure given by industry for the time required for development of a single pharmaceutical product has been 15 years, on average, though some portions of that time span are being shortened in different ways. The 1992 Prescription Drug User Fee Act (PDUFA/PL 102-571) made it possible for the FDA to reduce its review time for new chemical entities (New Drug Application [NDA]) from 32 months in 1992 to 17.8 months in 1996;[26] the effect of PDUFA on development time for drugs and biologics is under study. Corporate mergers are also restructuring industry R&D strategies and structures, in an effort to cut costs, save resources, and bring products to market more quickly. The total span from bench to market remains long, nevertheless, and the Collaboration on Drug Development Improvement (CCDI), yet another agency/industry/academic collaboration, has been charged with answering the following, generic question: Where does drug development time go? The question assumes paramount importance in the context of emerging infections. The earlier example of the speedy development of the first antiretroviral is inspiring but, so far at least, singular. All things being equal, were today ground zero for a new and lethal disease, by current standards the first medicinal therapy might not be available until 2012.

Another element in industry R&D decisions is the degree of predictability across the product cycle since, like time, unpredictability has financial implications. The research itself may pose unique and unforeseeable technical problems that produce delays, if not frank failure. In areas of societal controversy such as reproductive health, drug abuse, and STDs, liability—always part of industry's profit projections—becomes weightier. In this connection, since STDs can be defined as emerging or reemerging diseases, in some instances in epidemic proportions, issues of liability need to be taken into account explicitly.

There is also the unpredictability associated with what industry perceives as undue government interference. A case in point is the Orphan Drug Act and

perceptions of the effects of the various congressional modifications to that legislation that were proposed beginning in 1990. Those modifications did not materialize but, as indicated in a more detailed discussion of the Act later in this report, just the prospect of change is said to have had a chilling effect, yet another illustration of the heavy role predictability plays as an incentive to industrial R&D investment.

A World Bank survey of high-level representatives from the pharmaceutical industry to ascertain industry involvement in developing products for infectious diseases identified additional barriers: (a) lack of adequate information about the basic research that is under way in universities, research councils, and biotechnology companies worldwide that could provide material for industry to screen to generate more product leads; (b) the costs and duration of clinical trials; and (c) limitations inherent in the developing country market for products that could deal with the diseases that primarily afflict those countries. The survey also elicited industry suggestions about ways to lower these barriers. These are incorporated into Table 2, which presents a categorized summary of ideas about incentives for increasing pharmaceutical research and development for priority infectious diseases.

LEGAL AND REGULATORY ISSUES*

Another area where disincentives to pharmaceutical research and development are said to reside is the legal and regulatory domain. Questions for the Forum have to do with the extent to which any of those disincentives applies to emerging infections, notably in connection with the widening range of threats from antimicrobial resistance and, more positively, whether there are incentives within that domain that could be brought into play.

The FDA recognizes that there are major problems with regard to resistant organisms and believes it appropriate to use all existing regulatory tools to address them. Its general strategy is to build as much as possible on mechanisms already available under existing regulations, specifically those mechanisms originally intended to expedite the development, evaluation, and marketing of new products for treating life-threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy exists. The purpose of this set of regulations reflects the FDA's determination to exercise the broadest flexibility in relation to such conditions and reflects a recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat such illnesses.

Those elements of this set of regulations that might be mobilized toward the development, availability, and optimal utilization of antimicrobial products fall

*This section documents the presentations and discussions pertaining to Element 3 of the workshop agenda, "Legal and Regulatory Issues."

under the rubric of "accelerated approval."[27] Of most interest are provisions fostering more rapid product review and greater flexibility in the design of clinical studies, including early and regularized communication between the agency and industry, expansion of the allowable universe of data sources, and utilization of surrogate endpoints. Another relevant mechanism within this category is approval with restrictions on distribution so as to ensure safe use; however, while such restrictions may well be beneficial in public health terms, their meaning in market terms may act as a disincentive to industry R&D investment.

There are other legal and regulatory issues that lie beyond this special category of exception that are consequential for emerging infectious diseases. These include the labeling of existing antimicrobials; product availability; international harmonization of pharmaceutical regulations; intellectual property rights; and another category of exception, "orphan drugs."

Accelerated Approval and Development of Drugs for Serious and Life-Threatening Illnesses

Clinical Studies

FDA approval of new compounds is often constrained by difficulties inherent in clinical trials. These may relate to getting enough cases of resistant organisms in a trial cohort to be able to demonstrate efficacy, or to circumstances where full-fledged clinical trials are simply not possible, for example, military and terrorist situations. FDA regulations for life-threatening illnesses allow for considering an approval action earlier in the development process; accelerating enrollment in clinical trials; and for aggregating efficacy data from such other sources as *in vitro* analysis, animal models, case series and historical controls, and qualified foreign clinical trials. Which data, in which combinations, will suffice for securing approval can be defined in early consultations among FDA officials, industry representatives, and expert advisers, meetings that can take place prior to submission of an initial Investigational New Drug application and/or at the end of Phase 1.[28]

Surrogate Endpoints

The FDA may also grant marketing approval for a new drug for serious or life-threatening illnesses on the basis of data from controlled clinical trials establishing that the product has effect on some surrogate endpoint that is reasonably likely, based on epidemiological, therapeutic, pathophysiological, or other evidence, to predict clinical benefit, rather than solely on the basis of effect on survival or irreversible morbidity.

The purpose of surrogates is to make products available to individuals earlier, a consequence that also acts as a commercial incentive. Surrogate markers

employed in the past have included antibody levels that anticipate protective efficacy, as in the case of many vaccines; CD4, viral and plasma RNA, and branched chain DNA as measures of impact on HIV seroconversion; lowered blood cholesterol and hormone replacement levels in the case of drugs for corresponding indications; and, most recently, sputum status as a surrogate endpoint for tuberculosis therapy.

When surrogate endpoints are allowed, final product approval is typically contingent on a requirement that the applicant study the drug further to confirm and describe its clinical benefit, thereby validating the surrogate(s). Promotional material is somewhat controlled during this interim period. The duration of follow-up studies may be shortened through prior agreement between the FDA and industry about what data approaches will be acceptable. Should the studies fail to confirm the validity of the surrogates, the regulations also provide for quick removal of the product from the market, although this is difficult for the agency in practical terms and probably disappointing to industry.

Restricted Distribution and the Matter of Antimicrobial Resistance

The accelerated approval regulations also carry an option for restricted distribution of a product if there is reason to think that it should be made widely available only after confirmatory studies have been implemented. Should the FDA conclude that even a product shown to be effective can be used safely only if distribution or use is restricted, it can require postmarketing restrictions that either limit distribution to certain facilities or physicians with special training or experience, or make distribution conditional on performance of specified medical procedures.

The question was raised as to whether restricted distribution might merit consideration as a strategy for preserving the viable life span of new antimicrobial drugs for resistant isolates. The question has no simple answer. Beyond the public health importance of controlling the evolution of antimicrobial resistance, on the industrial side it is just common sense that when major investments are made in developing new products, it is reasonable to expect them to remain useful for their unique indications for some period of time. At the same time, while restricting the distribution of new antimicrobials might well serve to extend their viability, it would also constrain the size of their market and, therefore, potential returns on R&D investment. In effect, conserving the viability of new antimicrobials is at odds with the need to stimulate development of those products. Another, related dilemma is the pressure that would be applied almost inevitably by individual patients or physicians for access to new antimicrobials, versus the need to conserve their value for the benefit of the wider community.

Even were restricted distribution to be invoked as an option, it is nonetheless an authority that is limited as indicated above and one that has been used by the FDA only very rarely. The Controlled Substances Act, another regulatory effort to restrict access, applies only to psychoactive substances and steroids. This leaves

labeling as the sole current regulatory mechanism for limiting use of antimicrobials.

Options in the clinical arena are only unevenly helpful. Infection control, formulary, and peer review committees may be present in different clinical settings, but each of these responds to different guidelines and cost considerations with regard to managing antimicrobial products. The fact that resistance cannot be immediately detected *in situ* using available tests, together with the fact that ongoing information about local trends in resistance, beyond those at a single health care facility, are hard to come by, is another significant obstacle. Absent such information, antimicrobials are prescribed presumptively and therefore, in some cases, inappropriately. The availability of rapid, low-cost diagnostics at the point of care would reduce such misapplications and would also serve the urgent needs of the public sector and industry for ongoing data on patterns of disease and the evolution of resistance.

All this suggests three avenues of pursuit. One would explore possible regulatory pathways toward safeguarding the usefulness of new antimicrobials that would not unduly dampen industry's interest in developing new products. Another would examine the implications of other kinds of national guidelines on clinical management of antimicrobials for the pharmaceutical and managed health care industries in terms of costs, drug utilization, and industrial R&D investment decisions. For example, when vancomycin lost patent protection in the late 1980s in the United States, the price per gram dropped rapidly as the number of grams increased markedly, although since the 1996 CDC recommendations on the appropriate use of vancomycin, growth in that use has moderated. Yet another avenue would explore and define the sorts of infrastructure required for keeping the evolution of antimicrobial resistance under some kind of reasonable control.

The issues involved in restricted use are also multisectoral, given the relationships between evolving resistance and antimicrobial use in animals and, recently, trees and plants cultivated for commercial purposes. The few efforts to restrict veterinary use of antimicrobials so as to retain their value for human health needs do not seem to have occurred in a systematic, cross-sectoral way. Nor have representatives from the food production and trade sectors, or from the pharmaceutical industry, been regularly engaged in the health sector's dialogue about a problem in which all have something to gain, something to lose, and something to contribute.

Product Labeling

Another issue for development of antimicrobial products lies outside the category of regulations addressed previously—the need for regular updating of the microbiology portion of labels so as to reflect changes in patterns of resistance in a timely way and convey that information to clinicians. Time is required for an initiating company to gather the data typically required for a label modification, for submission of information to the FDA, agency review and approval, and label

printing and distribution. On the user side of the labeling equation, the primary print media such as the *Physicians' Desk Reference* and *Morbidity and Mortality Weekly Report* may not reach or be readily used by clinicians, even when available on-line.[29]

A fundamental problem, for industry and for public health in general, is what was described as "the woeful state of U.S. national surveillance of drug resistance in most community-acquired pathogens"—for example, drug-resistant *Streptococcus pneumoniae*. Implied here is the need for a comprehensive, integrated system, some sort of national clearinghouse or database that would, first, regularly collect resistance data from numerous sources, including clinical services and industry clinical trials, in the United States and offshore. Second, the system would redistribute the information to all entities concerned. The public health value of such a system would seem obvious. What may be less obvious is its great significance for industry's ability to estimate the market demand for antimicrobial products that would drive R&D processes forward correspondingly.

Nonetheless, lack of funds was described as a problem at every imaginable level of surveillance. The budget for WHO's pivotal role in bringing together the different surveillance networks worldwide is $17 million, an amount generally seen as insufficient. The CDC appropriation for FY1997 was $44 million out of the $125 million estimated as needed annually to implement its Emerging Infections Strategy, the first component of which is addressing surveillance and response needs. [30] Funding at the state level, even in states that are disposed to support infectious disease programs and that have been designated as CDC emerging infection program (EIP) sites, is inadequate. In Minnesota, for instance, 88 percent of all money for infectious disease epidemiology surveillance is soft money and there is no permanent infrastructure in place.

Product Availability

The FDA is often able to play a facilitating role in situations of drug shortage. Although little appreciated, the role is potentially important in some instances of emerging infections. An instructive case, in which both the FDA and the CDC played a crucial part, was the response to the resurgence of tuberculosis (TB) that became so painfully apparent at the beginning of the 1990s, at the same time that the supply of drugs for treating the disease had dwindled drastically. The widespread belief that TB was "cured" had acted to depress continued manufacture by large pharmaceutical companies; the overall number of suppliers, both of finished product and raw material, had dropped precipitously; and modernization of manufacturing processes had, in some companies, obliterated their capacity to make older products. Resolving each of the parts of this problem required finding and obtaining drug, domestically and offshore, from several smaller and larger companies; developing requirements for manufacture that would be flexible yet not compromise product quality; and mobilizing publicand private-sector distribution channels. The time required to replicate these processes in comparable

emergency situations in the future would vary widely, depending on availability and location of existing product; need to manufacture; the financial and organizational ability of other public-sector entities (e.g., the CDC) to collaborate; the seriousness of the disease and size of the affected population; and the risk to the wider community.

International Harmonization of Technical Requirements to Register Pharmaceuticals

As indicated earlier, the FDA has the statutory authority to utilize data generated through clinical trials conducted outside the United States.[31] The acceptability of results from such trials depends on their having been well designed and well conducted by qualified investigators in accordance with ethical principles acceptable to the world community. [32] However, maybe because of misconceptions or the lack of existing infrastructure, the impact of that authority on new R&D seems to have been small.

In contrast, the International Conference on Harmonization (ICH), an initiative started in 1990, was deliberately multilateral. Its purpose was to develop, in a formal process, agreement among regulatory authorities and industry representatives from the European Community, Japan, and the United States on harmonizing technical requirements for registration or product approvals so that a pharmaceutical company could submit the same, single, core data package to the corresponding regulatory bodies. Beyond the subtle benefits from more open, more regularized communication, the guidelines produced since establishment of the ICH have proved effective in reducing duplication and the numbers of animal and human subjects involved; they have also harmonized guidance concerning complexities related to dose response, policies for some special populations, and selection of controls. Work is ongoing in harmonizing statistical principles for clinical and placebo-controlled trials; design of studies; reporting of adverse reactions; addressing ethnic and gender diversity in pharmacogenetics and metabolism; developing an international medical terminology; and establishing standards for electronic transfer of data.

The trend toward harmonization, in specific product lines and in related areas such as the development of veterinary products, should shorten product development cycles and thereby act as a positive incentive to global pharmaceutical R&D, at least in general terms. How harmonization could serve the known and possible demands of emerging infections remains unspecified.

Intellectual Property Rights Revisited

In the case of emerging infections, lack of patent protection may be acting as a major disincentive in at least one possibly important respect. Among the hundreds of potential antibiotics left undeveloped on company shelves, some compounds

might, in theory, offer new product leads. Nonetheless, because they have gone off patent and are therefore unprotected in any prospective market, there is little justification for developing them further. A debated issue, perhaps meriting future exploration, is whether the number of such compounds is significant or, when factors such as cross-resistance are taken into account, their true potential is actually quite small.

A related matter is whether, even with all things equal on the patent scene, industry would consider it worthwhile to target a single resistant mechanism, for example, methicillin-resistant *Staphylococcus aureus* or even vancomycin-resistant staphylococci, for which the markets are not seen as large enough to justify investment. The burgeoning trend is for large pharmaceutical companies to seek collaborations with genomics companies, with the immediate objective in mind of bringing in new targets showing no cross-resistance to compounds that already exist and that retain activity against older targets. The ultimate objective of this strategy is to develop agents that have a wider spectrum and are therefore more likely to have a larger market and longer useful life.[33]

The patent system is not the only source of protection for pharmaceuticals. There are provisions through the FDA, under the Patent Term Restoration Act,[34] that grant a period of exclusivity for the first developer of a product, even if the product has gone off patent. Under the act, an Abbreviated New Drug Application (ANDA) process is made available to a generic competitor who is allowed to rely on the safety and efficacy data of the product innovator. For drugs containing an active ingredient not previously approved by the FDA, the innovator is protected from generic competition by the ANDA process for a period of 5 years from marketing approval. If the active ingredient has been previously approved by the FDA and new clinical studies are essential for the approval of the product, then the innovator is protected from ANDA generic competition for a period of 3 years from marketing approval. Two limitations inherent in the act reduce its value as an incentive for companies to pull existing compounds with expired patents off their shelves for application to emerging infections. One is that, in general, a 5-year or 3-year period of exclusivity is insufficient to justify the expense associated with clinical trials. Second, the act excludes antibiotic drugs such as penicillin and streptomycin that are produced by fermentation of microorganisms for which batch certification is required to insure safety and efficacy.

Orphan Drug Legislation

The Orphan Drug Act (PL99-91) was passed in 1983 to encourage development of drugs then known to be effective against rare diseases or conditions, which were defined as those affecting fewer than 200,000 people in the United States. In the case of a vaccine or drug intended for diagnosis or prevention of such a disease or condition, the persons to whom such a drug would be administered in the United States must be fewer than 200,000 per year.[35] A broader underlying assumption was that there was no reasonable expectation that

the costs of drug development and marketing would be recovered in future sales of the drug in the United States. The act allows sponsors to request orphan drug designation for a previously unapproved drug or to request a new orphan indication for an already marketed drug, and also permits treatment use of investigational orphan drugs. Most importantly, it promises 7 years of exclusive marketing for the first orphan condition to receive FDA approval.

Since the act's passage, there have been 663 orphan product designations by the FDA, including antibiotics, antivirals, vaccines, and immunoglobulins. Of that number, 102 (15.4 percent) were for infectious disease designations. And, of those, 14 (14 percent, or 2 percent of the total number of designations) were for tropical diseases. An unknown number of these were "orphans" in the U.S. context but might have much broader application overseas. In an ad hoc survey by PhRMA of its member companies, the 11 companies that responded reported 7 applications pending at the FDA for orphan indications, plus 7 Investigational New Drug (IND) applications and 21 pre-IND projects intended for orphan indications. Of the 53 drugs approved by the FDA in 1996, seven (13 percent) were orphan indications.[36]

The FDA also issues grants under the act, the funds for which come out of its own budget and represent a direct subsidy from the agency for research on rare diseases. Since the beginning of the program, there have been about 300 such grants, with a total dollar level in 1996 of $12 million. Six of those 300 grants, or 2 percent, were for infectious disease.[37] Although both grants and orphan designations require a United States consignee or agent, application for orphan status is not limited to U.S. products.

The legislative experience of the act has been uneven. Over time, unexpected uses of its provisions have evoked public and congressional complaints about price, lack of competition, unjustified exclusivity, and the sizes of target populations. Beginning in 1990, Congress proposed various pieces of legislation that would remove or limit sponsor incentives for orphan drug development at such time as a given orphan population increased—as in the case of HIV/AIDS—or when off-label use had the effect of making a given orphan product more lucrative. Pricing issues were at the center of the debate and price caps were among the legislative constraints considered. Although no legislation ensued, the mere prospect of price caps served to stifle designation and approval rates and rare disease research in general is said to have suffered.[38]

There have been attempts to replicate the Orphan Drug Act, in the case of drugs for treating drug abuse in 1990 and for pediatric indications in the 104th Congress. Neither bill was enacted. Whether the act might be somehow applicable for fostering development of products for emerging infectious diseases would depend on the purpose of such application. If, for example, there are many products in the R&D pipeline, perhaps an infectious disease equivalent to the Orphan Drug Act might spur those products to market and thus justify further consideration. If, however, the objective is to stimulate research on entirely new classes of products to diagnose and treat infectious disease, an orphan drug clone would be inappropriate and legislatively improbable. Major companies may develop drugs for an orphan indication without requesting orphan designation.

The proposition was advanced that congressional concern about emerging infections might be mobilized to address a range of possibilities, for example: (a) an enhanced basic research agenda on immune response mechanisms; (b) more comprehensive surveillance of infectious diseases, especially foodborne pathogens; (c) a major public education campaign to promote more judicious use of antibiotics by both patients and physicians; and (d) options for energizing product development for niche markets.

PUBLIC-SECTOR AGENDAS AND PRIORITIES*

The R&D agendas of key public-sector entities—their priorities, program implementation, collaborations, budget allocations, and issues for the future—were presented at the workshop in a series of thumbnail reports on each agency's activities in the area of emerging infectious diseases. These are presented in Appendix A. The institutional priorities of each public-sector entity are also mapped in Table 3.

Several aspects of public-sector activity are quite clear from these two summaries. One is that there is no pattern of priority commitments to any single disease. Overall, public-sector thinking is oriented toward foundation issues: encouraging basic science and its translation into products; understanding and strengthening systems; gathering and disseminating good data; and, throughout, seeking participation by the private sector and developing the contexts that will make that possible. By these accounts, the public sector has not yet developed a list of emerging infectious diseases that might constitute the kind of R&D "menu" that some industry representatives have indicated could be useful. The questions of whether such a list is possible, whether such a list might serve to guide industry developmental activity or whether, in that connection, such a list might serve as the basis for a series of market analyses, were not asked at the workshop but could be worth posing.

LESSONS LEARNED AND ISSUES FOR RESOLUTION

This workshop set out to extract from experience ideas on how best to assure availability of pharmaceutical products needed to address emerging infectious diseases, particularly those products most likely to be orphaned by the customary workings of the market. Because the CVI continues to be a learning process, it served well as a case study. Industry and other public-sector perspectives then enlarged upon lessons from the CVI, provided other case material, including useful learning from experience with HIV/AIDS, and added understandings about

*This section documents the presentations and discussions pertaining to Element 1 of the workshop agenda, "Thumbnail Reports: Public-Sector Priorities and Relevant Activities."

options and the large dilemmas that remain. Table 2 (see the Summary) synthesizes all these workshop perspectives and might be considered as a map of core incentive areas for targeted efforts in the future.

Lessons from the Children's Vaccine Initiative

Divergent Sectoral Mandates and Notions of Risk

The overarching lessons the founders of the Initiative had to internalize were the legitimacy of economics as the driver of the industrial sector; the size of the costs of developing and producing vaccine according to good manufacturing practices; and the obligatory linkages among costs, time, and predictability in the processes of research, development, production, and market revenue growth. Another important lesson for the public sector was reinforced in the conclusions of the CVI/Rockefeller Bellagio meeting, namely, that the public-sector international organizations still have much to do to fulfill their responsibilities in the public/private partnership, including, importantly—but surely not limited to—providing earlier estimates of demand for public health products and fully engaging in well-articulated advocacy for public health needs.

An ancillary fundamental was acknowledgment of what are basic disparities between the two sectors in the understandings of risk. In public health, risk derives primarily from epidemiology. For industry, in this case the pharmaceutical industry, risk is ultimately an economic function. Industry wants as much predictability and consistency as possible when it makes its R&D investment decisions, especially when profit margins are likely to be narrow. Thus, lack of sufficient, reliable, and decisive consensus about public-sector needs, priorities, and policies may well dampen prospects for private-sector collaboration.

A next step is figuring out how to share divergent risks. This implies sharing costs and other resources, as well as acting on the recognition that both sectors typically must deal with political risks and with the risks, real or perceived, of making a mistake, both of which can lead to excessive caution. As elementary as all this may seem, none of these notions had been part of the standard catechism for some of the CVI "pioneers," whose professional lives had been spent in the public health sector.

The Product Life Cycle and the Role of Market Analysis

Research and development is a total process, a pushing and pulling between demand and supply that ultimately connects laboratory and consumer. The CVI gradually implemented its recognition of the need to understand, define, and explain the market for publicly needed products, since it is in the marketplace that the interests of the two sectors ultimately coincide. This requires well thought out, timely, and inclusive epidemiological, market, and cost-effectiveness analyses on

which to build public-sector strategies and readjust industry perceptions of market potential. It also means early interventions to make a given market more attractive to investment, in effect creating that market by limiting demand uncertainties and generating appealing economies of scale. This has involved tactics such as price tiering and attempts to enhance market exclusivity, all possibly relevant to emerging infectious diseases, some still incompletely resolved, none simple.

Authentic Collaboration

Particularly difficult was learning to implement collaboration in ways that go beyond rhetoric. The CVI experience resonates with the value of beginning partnerships very early and sustaining them with frequent, regular interactions at several institutional levels. Experience indicates that there will continue to be particular challenges in sharing information not typically shared such as information about what is well back in industry's R&D pipeline, about potential scientific leads residing in the nonprofit sector, and about private-sector pricing rationales. Another challenge relates to sharing certain types of information more speedily and more often, for example, information from clinical trials and from the ongoing processes of priority-setting in the public sector, especially when those entail crucial shifts.

There are now interesting models of "sharing" within the private sector. Industry's "Inter Company Collaboration" on HIV/AIDS therapies also suggests options for cooperation within the private sector toward public objectives, a very new approach.

The Pivotal Roles of Advocacy and Public Information

A lesson still being learned, and much informed by ongoing instruction from the HIV/AIDS campaign, is the quintessential value of advocacy and public education in promoting public health priorities and catalyzing public awareness. This is a role highly suited to the public and nonprofit sectors but rarely truly or fully utilized by the former and not easy to fund.[39] Advocacy for the importance of vaccines in general and for the need to develop new vaccines for existing and prospective epidemiological requirements remains largely unimplemented.

TABLE 3 Public-Sector Priorities for Addressing Emerging Infections

	State Health Depts.	CDC	DARPA	FDA	NIAID	DOS	VA	World Bank
Surveillance and response	X	X	X			X	X	
Basic research	X		X	X	X		X	X
Applied research	X	X	X	X	X	X	X	
Prevention and control	X	X			X	X	X	
Public health infrastructure	X	X			X	X	X	
Public education	X	X		X		X		
Promote global preparedness		X	X			X		
Product availability		X		X		X		
Engagement of private sector		X	X	X	X	X		X

Although many lessons from the CVI have been converted into effective action, issues inevitably remain. Much of the Initiative's energy has been dedicated recently to catalyzing developing world access to vaccines already in limited use, a focus justified by the need to solve immediate problems of vaccine introduction so as not to generate a backlog of under-used vaccines. The point was made that the original notion of creating and licensing a brand new, single-dose, oral, multivalent vaccine was somewhat deflected by the gradual recognition that vaccines for many of the major causes of morbidity and mortality in developing countries were already being developed for industrialized markets. Although a return to that early focus will require a different set of processes, it is one for which industry has all the necessary tools. The concept was advanced that what may be needed is the development of a broad portfolio of potential components at different stages of development, where a number of risks have already been resolved by the public- and nonprofit-sector R&D through early-stage trials. The latter is the future challenge the CVI faces and for which its half decade of experience has been, in effect, a practice session.

Issues for Resolution

Other issues arose in the workshop that go beyond vaccines and were identified as being of special, even profound relevance to emerging infectious diseases, especially when those diseases are likely to be commercial orphans. In their majority, these are areas of tension concerning mechanisms that could stimulate the research that is most directly necessary for addressing emerging infections, but that are somehow problematic.

Agendas and Priorities

Although each public-sector institution is *sui generis* and driven by different basic mandates, there seemed to be general agreement among the public-sector participants in the workshop about the broad areas of programmatic importance for dealing with emerging infections. What did not emerge as anticipated was a list in response to industry's expressed interest in clear portrayals of specific disease priorities, although HIV/AIDS, tuberculosis, and malaria would now seem to be obvious enough. Given the difficulty inherent in predicting the arrival and future significance of emerging infections, any such list is necessarily limited to "arrived" diseases about which there is already justification for concern. The rest, as the public-sector agendas summarized in Appendix A suggest, is being categorically prepared.

Two alternative responses to industry's need to know were advanced.

1. Well-articulated agendas for development of generic requirements, for example, diagnostics that could not only identify pathogens but assess development of resistance, or multiagent therapeutics;
2. Surveillance systems integrated and configured so as to be, continuously and formally, accessible to all interested parties. The value added to the second alternative would be the base it would provide for more rapid and efficient updating of labeling for antimicrobials, another highly important problem that remains unresolved.

Funding

Inadequate funding appears to be an issue at every level of infectious disease surveillance, as evidenced in insufficient infrastructure, inability to support recurrent costs, or both. These problems are not exclusive to the developing world; the surveillance capability of the United States is similarly threatened. The subject of emerging infectious diseases has commanded interest in the U.S. Congress that has resulted in additional allocations for addressing the issue. However, today's pressures for public-sector austerity augur poorly for future increases, particularly with regard to global requirements. Two major areas of U.S. contribution to global health are problematic: (1) official development assistance (ODA) and (2) investment in research and development for those diseases that dominate the needs of developing countries. Beyond the matter of inadequate absolute amounts, funding instability is a critical problem, especially for research and development, characteristically a long-term endeavor.[40] Erratic funding also hampers maintenance of infectious disease epidemiology surveillance of the quality needed to properly inform both the public health and industrial agendas.

Multi-Tiered Pricing

Price tiering, in conjunction with new approaches to market segmentation and high-volume commodity procurement, could serve the needs dictated by certain infectious diseases. At the same time, despite its potential leveraging role, differential pricing carries considerable political freight. The public sector has yet to refine arguments that might be made usefully to policy makers, not just in the United States but in other countries that question the appropriateness of the mechanism.

Restricted Distribution

Any imposition of restrictions on the distribution of products that acts to constrain their market share for a significant period of time is an obvious economic

disincentive to industrial investment in developing new products. This disincentive is unlikely to be overcome by imposition of higher prices to compensate for lost volume. Whether the longer useful life that can be achieved by limiting utilization of an antimicrobial product would act as adequate compensation does not seem to have been analyzed. The tension between responsible marketing and reasonable profits is high; the importance of getting a handle on this topic was agreed to be similarly high.

Surrogate Endpoints

The identification and use of surrogate endpoints has been critical for developing new products to address the AIDS pandemic and is part of the FDA strategy for accelerated approval of certain product classes. The development of generic categories of endpoints that might be used in connection with a range of infectious disease endpoints is an issue awaiting consideration, as is the development of alternatives to correlates of protection for vaccines against diseases for which clinical trials would be difficult or even impossible, for example, the case of Ebola virus or pathogens used in biowarfare or bioterrorism.

Patent Extensions

Lack of patent protection has been identified as a disincentive to developing new antimicrobials using unexplored compounds that have been abandoned by pharmaceutical companies. Because these are now off-patent and are therefore insufficiently protected from competitive market forces, there is little reason to pursue them further. Existing protections are viewed as insufficient, given R&D costs.

Extension of patent protection in these circumstances could conceivably be motivating for patent holders. On the other hand, would-be generic competitors might be expected to oppose such extensions. Thus, as a minimum, a delicate balancing of interests would be required. However, both the general notion of patent extension for abandoned compounds and its specific implications remain unexamined as possible incentives for development of infectious disease products.

Technology Transfer and Local Production

As a way for developing country markets to acquire better access to good quality health products, technology transfer for local production of those products has often disappointed, largely because of the unreliability of local infrastructures on which advanced technologies are highly dependent. On the other hand and somewhat ironically, the success of technology transfer may prove to be a problem, since it may cut into market share for imported products. In the case of

infectious disease products where a key technology is not readily transferable, this is not an issue; however, for older, lower-cost technologies, local production does become a factor in diminishing market appeal. The question of how big an issue this may be for emerging infectious diseases has not been asked and may be, with the possible exception of drugs for tuberculosis, largely premature.

Orphan Drug Designation

Work remains on the subject of the potential of orphan drug designation for at least some emerging infectious diseases. As the legislation is written, there would seem to be elasticity in terms of diseases affecting very small U.S. populations, at the same time that non-U.S. populations, specifically developing world populations suffering from those diseases, might be quite large. Furthermore, even though congressional receptivity to utilization of orphan drug legislation for generic public health needs has been limited, prospects for orphan drug designation seem to be more likely when the objective is to spur products already in company pipelines to market. The challenge is then to define what products are needed for what emerging infectious diseases and to seek to make a match with what industry may have in relevant pipelines. This is obviously a topic for continuing intersectoral conversations.

Other Topics

Other topics for such conversations might well build on reported congressional interest in an enhanced basic research agenda on immune response mechanisms; more comprehensive surveillance of infectious diseases, especially foodborne pathogens; a major public education campaign to promote more judicious use of antibiotics by both patients and physicians; and options for energizing product development for niche markets. Each of these, like the potential for orphan drug designation, might well reward more precise focus and articulation than has been the case so far.

A Final Observation

The scientific quandaries posed by complex diseases like malaria, STDs, and HIV, as well as the entire matter of antimicrobial resistance, are daunting. In addition, while the market system has served well, it engenders a sometimes fierce adversarial environment, in which the interests of each party—not to mention the overall public good—are often submerged in the service of emotion-laden stereotypes and external forces. Each of the parties—labeled generally as industry, government, and the consuming public—still has a way to go in articulating its vision of the optimum outcome as the elements of a rational policy confrontation.

Still, the strategies and learning from the CVI, from HIV/AIDS, and from the many mechanisms described in this report, offer plentiful options for stimulating research and development on products for emerging infectious diseases, at least some of which will be, for one reason or another, orphans that will need to be adopted creatively.

NOTES

1. Institute of Medicine. *Contraceptive Research and Development: Looking to the Future*. PF Harrison, A Rosenfield, eds. Washington, D.C.: National Academy Press, 1996.

2. R Twombly. The future face of disease. *Environmental Health Perspectives* 105(2):184–186, February 1997.

3. The CVI now defines itself as "a coalition committed to expanding protection against infectious diseases, particularly through the development and introduction of new and improved vaccines" (CVI Secretariat, Conclusions from the CVI/Rockefeller Foundation Bellagio Conference on the Global Supply of New Vaccines, 2–7 February 1997, Geneva, World Health Organization, 1997).

4. A number of explanations have been offered for the vaccine renaissance, all of which probably apply. These include industry's gradual appreciation of the potential of the National Vaccine Injury Compensation Act passed in 1986; great advances in molecular and cellular biology and biotechnology, and the promise of genetically engineered vaccines; dedicated efforts to develop vaccines for such key needs as AIDS prevention; understandings about the infectious etiologies for some chronic diseases; greater awareness of the cost-effectiveness of vaccines as a public health measure; WHO's Expanded Program on Immunization (EPI) and a better than doubling of the number of vaccine doses purchased by UNICEF beginning in 1985; and growing concern about antimicrobial resistance (Institute of Medicine, 1996).

5. At the Summit, it was proposed that the ideal CVI vaccine should be given as a single dose (preferably orally); contain multiple antigens; and be affordable, heat-stable, effective when administered near birth, and effective against diseases not currently targeted (Institute of Medicine. *The Children's Vaccine Initiative: Achieving the Vision*. VS Mitchell, NM Philipose, JP Sanford, eds. Washington, D.C.: National Academy Press, 1993).

6. World Health Organization. Summary and Conclusions, and Presentation on Sustainable Vaccine Supply/Global Targeting Strategy and Market Segmentation: Tiering Vaccine Prices. Children's Vaccine Initiative/Rockefeller Foundation Bellagio Conference on the Global Supply of New Vaccines, 3–7 February 1997.

7. Mercer Management Consulting. *Report on the U.S. Vaccine Industry*. Commissioned by the Department of Health and Human Services, 1995. New York: Mercer Management Consulting. *Summary of UNICEF Study: A Commercial Perspective on Vaccine Supply*. New York: Mercer Management Consulting, 1994.

8. As of this writing, UNICEF has not found the funds it needs to purchase Hib vaccine.

9. In fact, most of UNICEF's purchasing from this group of suppliers is from a subset of the group. The balance of the traditional vaccines needed in the developing countries is satisfied through procurement and local production.

10. While the following points were not raised at the Workshop, it seems important to raise them here as items for future analysis. The Mercer report did not address at least two issues that are especially relevant to emerging infectious diseases. The first question is whether benefits from economies of scale will apply to new vaccines; for example, increasing lot size for vaccines involving conjugation technology may be more complex and costly than for the current vaccines. The report also did not determine whether prices offered by donor agencies would be sufficient to induce manufacturers to alter *existing* programs for vaccines under development, where alternative formulations might be more appropriate for some circumstances (Hausdorff 1996; WP Hausdorff. Prospects for the use of new vaccines in developing countries: Cost is not the only impediment. *Vaccine* 14(13):1179–1186, 1996).

11. Contract extensions, in a manner not dissimilar to patent extensions, can have the effect of reducing market competition, a dynamic perhaps worth noting in future strategy discussions.

12. The question of what constitutes a "reasonable rate of return" is of course elusive, highly dependent on individual and sectoral perspectives, and obviously a matter for lengthy debate, debate in which the Forum did not engage.

13. United States Senate. Hearing to Review Federal and State Expenditures for the Purchase of Children's Vaccines. Subcommittee on Investigations and General Oversight, Committee on Labor and Human Resources, July 22. Washington, D.C.: U.S. Government Printing Office, 1982. — WJ Clinton. Statement at the Fenwick Center Health Clinic, Arlington, Virginia, February 12, 1993.

14. There are two major classes of buyers of childhood vaccines in the United States: the public sector, including federal and state governments, and the network of private-sector physicians, hospitals, pharmacies, and clinics across the country. The federal government, through the Centers for Disease Control and Prevention (CDC), negotiates a bulk purchase price for priority vaccines with key at rates substantially lower than those listed in the private sector. The CDC then makes grants to the states to purchase the vaccines, passing on the lower prices. Over the past decade, the public sector has purchased an increasing share of childhood vaccines, a trend to which industry objects vigorously as a major disincentive to innovation. Calls for universal federal vaccine purchasing have been of special concern (Institute of Medicine 1993).

15. The transcript will show that Forum members representing industry recused themselves from any discussion of price.

16. MR Hilleman. Cooperation between government and industry in combating a perceived emerging pandemic: The 1976 swine influenza vaccination program. *Journal of the American Medical Association* 275(3):241–243, January 17, 1996.

17. This information did not emerge in the workshop but was subsequently provided as supportive material by one of the participants. Sources: M Kane, J Clements, D Hu. Hepatitis B. In *Disease Control Priorities in Developing Countries* . DT Jamison et al., eds. New York: Oxford University Press, 1993, for the World Bank.

18. Institute of Medicine. *Vaccines Against Malaria: Hope in a Gathering Storm*. PK Russell, CP Howson, eds. Washington, D.C.: National Academy Press. 1996. In some respects, this study was a by-product of an earlier IOM study on this topic (Institute of Medicine. *Malaria: Obstacles and Opportunities*. SC Oaks Jr. VS Mitchell, GW Pearson, CJ Carpenter, eds. Washington, D.C.: National Academy Press, 1991).

19. The 10 April 1997 issue of *Nature* cites the comment by a researcher at the Institute Pasteur that it is ironic that companies should abandon malaria drug discovery just when assays for screening for active drug compounds are much more sensitive than in the past, and when genome research and molecular studies are yielding new targets for rational drug design. However, the industry view cited in the same article seems to be that even though basic research is at last producing truly interesting leads, it has not progressed sufficiently to be anything but a costly and risky business.

20. The large vaccine manufacturers, SmithKline Beecham and Pasteur Mérieux Connaught, still work on malaria vaccines and several biotechnology firms remain engaged in cutting-edge work (Chiron, Virogenetics, Vica), although others (e.g., Merck, Sanofi, Behringwerke, and Rhône-Poulenc Santé) have withdrawn from the area. Global spending on malaria research by the public and nonprofit sector has been declining over the past decade, although new infusions from the Wellcome Trust, WHO, and NIAID, and hoped for infusions from the World Bank are brightening the picture somewhat (D Butler. Time to put malaria control on the global agenda. *Nature* 386:535-541, 10 April 1997).

21. As this was being written, major coverage in the 10 April 1997 issue of *Nature* reported that discussions begun last year between the World Bank and WHO have expanded and there may in fact be a multiagency, 30-year program to control malaria, currently entitled "The African Malaria Initiative." At a meeting in January 1997 in Senegal, the Pasteur Institute; Medical Research Councils of the United Kingdom, Netherlands, and European Commission; NIAID, CDC, U.S. Army; and others, met to try to define a research agenda for malaria in Africa. The question of whether the program would fund research directly is still open; NIH Director Harold Varmus is talking about formal partnerships among the world's major research bodies in that connection.

22. DNA vaccines, also known as "naked DNA vaccines" or "genetic immunization," are being studied for many diseases including hepatitis, influenza, malaria, and tuberculosis. For several reasons, DNA vaccines are said to be one of the few HIV vaccine approaches that have potential to be distributed worldwide at reasonable cost (*International AIDS Vaccine Initiative Newsletter* 2(1), Winter 1997)

23. Of the 38 vaccines and 25 antivirals, 10 and 14, respectively, were for sexually transmitted diseases, including herpes simplex, hepatitis B, human papillomavirus, pelvic inflammatory disease, and cytomegalovirus. (Pharmaceutical Research and Manufacturers of America, *New Medicines in Development for Infectious Diseases: 1996 Survey*, Washington, D.C., 1993.)

24. The same ranking held for the biotechnology subsector, reflecting what is happening farther back in the R&D pipeline (KB Lee Jr, GS Burrill. *Biotech 96: Pursuing Sustainability*. Vienna, VA: Ernst and Young LLP, 1996).

25. Agouron, AB Astra, Aji Pharma USA, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Ciba-Geigy, DuPont Merck, Gilead Sciences, Glaxo Wellcome, Hoechst AG, Hoffman-La Roche, Merck, Pfizer, Pharmacia & Upjohn, Sigma-Tau, SmithKline Beecham, and Triangle Pharmaceuticals.

26. In 1996, 53 new drugs were approved in an average time for each of 17.8 months. Thirty-six of those were designated for "standard" review and were reviewed in an average of 19.7 months, and 17 were rated for "priority" review by the FDA and had an average review time of 13.7 months. Finally, of the 17 priorities, 15 were approved under user fees and had an average review time of 10.5 months. (JF Beary, III. *The FDA User Fee*

Program. Washington, D.C.: Pharmaceutical Research and Manufacturers Association, 1997.)

27. Food and Drug Administration. Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses. 21 CFR Ch. 1 (4-1-96 Edition): Part 312, Subpart E, §312; Part 314, Subpart H, §314.

28. Since the date of the Forum's February workshop, the FDA has proposed a "New Use Initiative" with the purpose of accelerating development of new and supplemental uses of medications in general. The Initiative would permit, as evidence for primary and supplementary approvals, utilization of all available data to determine the effectiveness of drugs and biological products. The Initiative provides anecdotal information about instances in which the FDA has already done this successfully and gives industry clear guidance on when the agency can decide that a drug is effective for a new use without the standard requirement for data from two new clinical trials. For example, in some cases a drug's effectiveness can be extrapolated from existing efficacy data, either from a new single trial supported by existing, related clinical data, or documented by adequate evidence from a single multicenter study (Department of Health and Human Services. FDA proposes New Use Initiative. *HHS News*, 13 March 1997).

29. The *Morbidity and Mortality Weekly Report* is already available on-line and the *Physician's Desk Reference* is supposed to be on-line by the end of 1997.

30. The $44 million is apportioned as follows: approximately 39 percent for surveillance and response, 17 percent for research, 19 percent for prevention and control, and 25 percent for infrastructure.

31. The term "sponsor" is used by the FDA to mean the entity that assumes responsibility for a clinical or nonclinical investigation of a drug, as well as for compliance with all pertinent regulations. A sponsor may be an individual, partnership, corporation, government agency, manufacturer, scientific institution, or an investigator regularly and lawfully engaged in the investigation of drugs.

32. Food and Drug Administration. Miscellaneous. 21 CFR Ch. 1 (4-1-96 Edition): Part 312, Subpart F, §312.120.

33. As this is being written, bills are before both houses of Congress to revamp the U.S. Patent and Trademark Office and fundamentally alter the rules that for 200 years have governed how U.S. patents are issued. Both bills would convert that office from a federal agency to a government-sponsored corporation and force many patents to be made public 18 months after filed, even if they have not yet been granted, whereas today U.S. patents are made public only after they are issued. The bill would also shield some technology users from patent infringement suits. Proponents, including many big businesses and groups that speak for the biotechnology and pharmaceutical industries, hail the changes as necessary to make U.S. patent law conform with international standards and put American companies on an equal footing with foreign rivals. Opponents, including many small inventors and universities, complain that the public disclosure rule would enable big companies to steal their ideas. Some patent experts and inventors claim that at least one of the bill's provisions impinges on the idea of government-protected exclusivity, which lies at the heart of current patent law (K Day. A reinvention of patent rules. *Washington Post*, Business Section, E1, E4, 24 April 1997.)

34. The purpose of the Drug Price Competition and Patent Term Restoration Act of 1984 (PL 98-417) was to restore part of the patent life lost during the regulatory approval process. It allows extension of the patent term to a period equal to the total time taken by the

FDA to review the new drug application plus one-half of the clinical testing time; it does not allow extension beyond 14 years of effective patent life.

35. Food and Drug Administration. Miscellaneous. 21 CFR Ch. 1 (4-1-96 Edition): Part 316, Orphan Drugs. *Act* means the federal Food, Drug, and Cosmetic Act as amended by the Orphan Drug Act. The limitation on population size is based on prevalence, defined as the number of persons in the United States diagnosed as having the disease or condition at the time of the submission of the request for orphan drug designation, in other words, confirmed cases.

36. Government Reform and Oversight Committee, Subcommittee on Human Resources, United States House of Representatives.

37. These are for single, discrete preclinical studies and clinical research on potential orphan products. They represent a direct subsidy for orphan drug R&D by the FDA and are administered by its Office of Orphan Products Development in a manner parallel to other Public Health Service grants. In almost all cases, the grants have been limited to a maximum of $100,000 in direct costs per year for up to three years. The program has grown steadily. In 1990, 65 recipients were allocated a total of $7.6 million; while for-profit, nonprofit, and government organizations are eligible, for-profit organizations represent a very small part of the total program. At the same time, the large majority of orphan designations have gone to drug sponsors that are not PhRMA members, in other words, to smaller firms. This suggests that the act may have served to enhance the participation of such firms in pharmaceutical research and development, thereby expanding the competitive pool (Office of Technology Assessment [OTA]. *Pharmaceutical R&D: Costs, Risks and Rewards*. Washington, D.C.: United States Congress, February 1993).

38. In this connection, FDA approval must be sought for *each* indication for which a company would like to market a given drug, a condition that some analysts define as yet another barrier (OTA 1993).

39. Though what has happened in advocacy for breast cancer research was not discussed at the workshop, it is very much a model. With several other examples of the role of advocacy, it is represented in the inventory in Appendix B.

40. The workshop participants' gloomy expectations seem well rooted in fact. In 1995, the United States spent about 0.1 percent of its gross national product on foreign assistance, a lower percentage than any of the other members of the Organization for Economic Cooperation and Development's Development Assistance Committee and less than Japan, France, and Germany in absolute dollars. Of the $9.9 billion spent on U.S. overseas assistance in 1994, just $1 billion was earmarked for health, primarily child survival and AIDS. The United States also remains in substantial arrears to those U.N. agencies that have health as a principal mandate, importantly including WHO. (Institute of Medicine, Board on International Health. *America's Vital Interest in Global Health*. Washington, DC: National Academy Press, 1997). At the same time, the World Bank's health portfolio, opened 15 years ago, has grown, so that the Bank is now the largest financier of international health. Its health portfolio in 1996 was $8 billion and is expected to grow by $2 billion annually over the remainder of this decade (Rockefeller Foundation, Social Science Research Council, Harvard School of Public Health. *Enhancing the Performance of International Health Institutions*: Pocantico Retreat, 1–3 February 1996. Cambridge, MA: Harvard Center for Population and Development Studies, 1996.)

APPENDIX A

Emerging Infectious Diseases Research and Development Agendas: Principal Public-Sector Institutions*

* This section contains thumbnail reports presented at the workshop on agency activities in emerging infectious diseases.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

R&D Priorities

Since it is hard to predict those diseases that may have future significance, worldwide and in the United States, CDC emphasizes preparedness. The CDC strategy for addressing emerging infectious diseases derives from recommendations in the 1992 IOM report and is structured around four goals:

Goal 1: To improve surveillance and response capacity.

Goal 2: To address applied research needs.

Goal 3: To strengthen prevention and control programs.

Goal 4: To repair public health infrastructure at local, state, national, and international levels.

Implementation

- CDC's extramural research program, halted in 1973, was reinstated at a level of $800,000 for FY97. Funding priority is assigned to research projects focused on:

— antimicrobial resistance (including mechanisms of resistance, development of better diagnostics, and strategies to improve prescribing practices); and
— tickborne disease (*Ehrlichia* and *Babesia*).

- Founding role in development and implementation of the CISET report.
- Organization and implementation of three sentinel networks: a physician network in collaboration with the Infectious Disease Society of America; one with the International Society of Travel Medicine; and one with a network of 11 academically based emergency departments in the United States, each focused on diseases and syndromes identified in their particular environment.

Collaborations

The CISET report represents collaborative thinking by 17 different federal agencies about how to work more effectively, together and with the private sector, toward implementing the CISET plan without duplicating efforts. At the operational level, interactions between CDC, NIH, FDA, and DOD are good.

Budget Allocations

CDC's core infectious disease budget decreased in real dollars through the 1980s into the early 1990s, but that trend was reversed in the last three budget years. The cost of implementing the CDC emerging infectious disease strategy is estimated at $125 million annually.

For FY97, the agency received an appropriation of $44 million toward implementation of the strategy, including international sentinel activity. The bulk of funds goes to domestic issues, but the plan is to allocate a higher proportion in each successive year to global needs.

CDC has requested an increase in the FY98 budget of $25 million, $15 million for emerging infectious diseases and $10 million for food safety.

Future Challenges/Concerns/Issues

- Continuing need to engage the private sector more effectively than in the past.
- Need to collect good data on drug resistance trends in community-acquired infections, since resistance appears to have been a factor in some of the mortality associated with pneumonia, diarrhea, tuberculosis, malaria, and perhaps HIV.
- The Public Health Service Act authorizes CDC to be involved internationally in epidemics and other unspecified high-priority situations. The agency, with the support of the Secretary of Health, has been trying to influence legislation that would provide a clearer international mandate, permit earlier involvement in crisis situations, and allow specific appropriations for international work, particularly as related to infectious diseases with a potential impact on the United States and to "bioterrorism."
- Aging, overcrowding, compromised security and safety, and general deterioration of the federal, state, and local public health laboratories.
- Need for a new laboratory for research on infectious pathogens requiring medium- to high-level containment.

DEFENSE ADVANCED RESEARCH PROJECTS AGENCY (DARPA)

R&D Priorities

Use of biological agents in combat and terrorist events, and development in some countries of offensive biowarfare capability motivated recent entry into biowarfare defense by DARPA, DOD's principal R&D agency. The overall goal of DARPA's Biological Warfare Defense Program is to reduce threat of biological weapons (including bacterial, viral, and bioengineered organisms) as factor in U.S. military operations. Its objective is to foster development of innovative technologies with potentially high payoff, even if also high risk, and to mobilize biotechnology industry capabilities to that end.

DARPA's R&D program in this area has four major thrusts:

1. Real-time sensing (detectors).
2. Informatics, with emphasis on integrating information systems into field awareness and logistics systems.
3. Advanced diagnostics: development of rapid diagnostic tests (e.g., array based) permitting real-time identification of responsible organisms/toxins and capable of diagnosing presently unknown or bioengineered agents (a new program).
4. Pathogen countermeasures (development of multiagent yet specific advanced therapeutics) to target common mechanisms of pathogenesis and functions or structures shared by groups of pathogens, or to modulate human biological response to pathogens; also interest in mucosal defense and countermeasures against toxins and mid-spectrum agents.

Implementation

- Broad agency announcements, with committed funding, in program areas; current solicitations, until September 1997, in pathogen countermeasures and advanced diagnostics.
- Information available on World Wide Web (http://www.darpa.mil).
- DARPA remains strongly committed to protecting proprietary business information and intellectual property rights of inventors. It has developed instruments to ensure inventors and producers of retention of those rights and to provide other incentives for commercialization, while also ensuring government access to the products involved. DARPA prefers to have most of its work open and publishable rather than classified. It has also been given special latitude with respect to regulations that have discouraged industrial involvement heretofore, and its legal and contracting offices have worked to reduce paperwork and adopt procedures more akin to standard commercial arrangements.

- DARPA is also dedicated to rewarding good performance with renewed and often increased support.

Collaborations

DARPA has a unique mission to anticipate and develop breakthrough technologies for the future, thus complementing work at other DOD agencies, CDC, and NIH.

DARPA has traditionally worked closely with other agencies and industry in microelectronics, materials science, and other high-tech areas. The agency hopes that its approach to targeting potential threats and focusing on mechanisms of pathogenesis or underlying mechanisms of disease will offer opportunities for commercialization and seeks to work closely with other agencies and the industrial community to help in transition of these products to commercial use.

Budget Allocations

DARPA is an extramural funding agency, its annual budget about $2 billion. An initial budget round allocated $20 million to the pathogen countermeasures program, with two more announcements (pathogen countermeasures and advanced diagnostics) in 1997, at about $25 to $30 million each).

Future Challenges/Concerns/Issues

- Developing partnerships (including an industrial advisory panel) with these objectives:

— fostering and sustaining liaisons with the industrial community;
— identifying promising new areas;
— keeping the agency abreast of state-of-the-art technologies;
— identifying gaps in DARPA's biological warfare defense program; and
— partnering on technology development and transition planning.

- Facilitating development of products resulting from the research it supports.
- Developing a community in the relevant R&D areas, with partners including industry, academic researchers, and government.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

R&D Priorities

NIAID has five goals in three broad areas.

Areas:

1. Increasing basic understanding of complex interactions among environment, microbe, and host influencing emergence.
2. Strengthening ability to develop and validate new prevention and control strategies.
3. Ensuring maintenance of research and training infrastructure adequate to meet current and future needs.

Goals:

Goal 1. To support application of scientific knowledge and new technologies to detection, identification, and interdiction of emerging diseases, by expanding research on ecological and environmental factors influencing transmission.

Goal 2. To support application of new discoveries and biomedical technologies to identification, management, and control of emerging diseases, by expanding research on microbial changes and adaptations influencing emergence.

Goal 3. To provide fundamental information for developing prevention and treatment strategies that can be employed to ameliorate disease impact, by expanding research on host susceptibility to emerging or reemerging pathogens.

Goal 4. To support development and validation of vaccines, therapeutics, and other control strategies for diseases with potential to emerge or reemerge.

Goal 5. To strengthen U.S. research and training infrastructure for detecting and responding to infectious disease outbreaks.

Implementation

- Program announcements, with funding behind them, to stimulate research in emerging infections.
- Support for special programs in areas such as clinical trials and international research.
- Allocation by NIH director of $3 million of own FY97 reserve to establish emerging diseases research networks that encourage interactions and collaborations among investigators working on related research issues, and to expand international research on emerging and reemerging diseases, including opportunities for young U.S. physicians and scientists to gain research experience working in areas where these diseases are currently found.

- Clinical and regulatory affairs group dedicated to interacting with the FDA on investigational new drugs, and harmonization.
- Support of intramural and extramural facilities for production of pilot lots of drugs and vaccines, toxicity and other preclinical testing, as well as clinical trials.
- Diseases being addressed through various funding mechanisms available to NIAID include arboviral diseases, aspergillosis, cholera, ehrlichiosis, emerging viral infections, hantavirus, *Helicobacter pylori*, hepatitis C, Lyme disease, measles, mycoses, plague, respiratory pathogens, STDs, streptococcal infections, and TB.

Collaborations

- Under U.S.-Japan Cooperative Medical Science Program, organized international conferences (1996, 1997) on emerging diseases, with State Department, USDA, CDC, Japanese Ministries of Health and Welfare and Foreign Affairs.
- Support of cellular pertussis vaccine clinical trials overseas.
- Awarded grant supplements for use of remote-sensing geographic information systems to predict infectious diseases distribution, in collaboration with NASA (FY95).
- Cooperative Research and Development Agreements and other less formal relationships with the private sector.
- Contracts with clinical trial groups, such as viral encephalitis, now expanded to herpes viruses and hepatitis; coordinated clinical trial network on fungal infections.
- Collaboration with Burroughs-Wellcome on use of acyclovir for herpetic encephalitis in infants (a small market).
- Collaboration with USAMRIID on antiviral compounds effective against Ebola.
- Organized U.S.-Italy conference on emerging diseases in 1997.
- Issued RFA and RFP for malaria vaccine development in collaboration with AID.

Budget Allocations

NIAID spent $334 million on non-AIDS infectious diseases research in FY96. Of this amount, $63 million was dedicated to emerging diseases research.

Future Challenges/Concerns/Issues

- Enhancement of complementarity and synergy between research and surveillance.
- Additional partnerships with private-sector firms and their greater capacities in development, importantly scale-up, chemistry, and manufacturing.

UNITED STATES DEPARTMENT OF STATE (DOS)

R&D Priorities

The State Department's interest in infectious disease is threefold. It is part of:

1. the economic agenda for foreign policy,
2. the science and technology agenda, and
3. the national security agenda.

State works to create conditions that are conducive for agencies to do science and technology research overseas, including promotion of international intellectual property rights, as well as tax and other incentives to R&D.

Infectious disease and its potential for counterterrorism are a growing concern for national security. State is working to safeguard infectious disease research activities within the foreign policy agenda. The department is also working to promote global preparedness within the context of infectious diseases, as part of both the national security and economic development agendas.

Implementation

State is involved in implementing a global infectious disease surveillance response network. Its strategy stresses use of embassy officials to understand and convey the importance of the connections between human health and healthy economic development.

As part of implementation of the NSTC/CISET Report on Emerging and Re-emerging Infectious Diseases, State is working with CDC and the White House Office of Science and Technology Policy to develop methods to bring the private and public sectors together to address the problem of supply shortages and strategies for quick response to emergency situations. Three CISET task force committees have been created to implement collaborative effort on setting up a global surveillance network:

1. Surveillance and Response, cochaired by CDC and DOD;
2. Capacity Strengthening, cochaired by CDC and USAID; and
3. Research and Research Training, chaired by NIAID.

Subcommittees have also been formed on:

- Antimicrobial Resistance, and
- Product Availability.

State is responsible for finalizing agreements for cooperative R&D arrangements and works continuously to create an environment that promotes voluntary compliance among nations.

In 1996 infectious diseases and HIV/AIDS were on the presidential agenda for the G-7 conference for the first time and commitments were made to collaborate to contain the spread of infectious diseases and work on a global surveillance network. At the 1997 G-7 summit, State will work to reinforce those commitments so as to translate them into provision of technical and financial resources.

Collaborations

State has international partnerships with the European Union under the new Transatlantic Agreement, whose agenda includes a focus on collaboration to contain infectious diseases. Similar efforts have begun with Japan, South Africa, and Russia, among others.

A U.S.-Brazil common agenda is being expanded.

Progress is being made with the Department of Commerce and the FDA to address product availability issues. A message is being drafted for the pharmaceutical industry to clarify the department's needs in this area and to suggest areas in which industry can assist in implementing department goals.

Budget Allocations

No data.

Future Challenges/Concerns/Issues

- To develop a composite message that stresses the importance of infectious diseases to each nation.
- To do better at defining public-sector interests and enhancing public awareness and knowledge of what the specific issues are, for the public and private sectors, in the United States and outside its borders.
- To create the conditions necessary for cooperation around the challenges of antimicrobial resistance.

DEPARTMENT OF VETERANS AFFAIRS (VA)

R&D Priorities

The VA's agenda is primarily domestic, one exception to which is a congressional mandate requiring the agency to back up the military in times of disaster, including use of weapons of mass destruction.

In the area of emerging infections, the VA will be working in three priority areas:

1. Surveillance, to obtain timely data of good quality that are essential to good demographic knowledge and making decisions regarding resource allocation.
2. Intervention, as a way to develop partnerships in communities and in VA facilities, and the development of common guidelines and tools for assessing outcomes in a standardized manner.
3. Research, with emphasis on areas of mutual interest to VA and DOD.

Implementation

The VA is working with two primary databases for its emerging infections surveillance initiative:

1. Annual Census. An annual census of all VA facilities has collected yearly data on specific diseases and provides good and fairly complete retrospective data. The cumbersome data-entry requirements for this census have motivated system improvements and further, dramatic improvements are expected as a consequence of the agency's new Emerging Pathogens Initiative.
2. Emerging Pathogens Initiative. This national tracking system will automatically extract specific data on pathogens and diseases of choice from VA computer systems nationwide and transmit them on a monthly basis to the appropriate location. Initially, data will be gathered on 14 diseases or pathogens, including bloodstream candida infections, *clostridium difficile*, cryptosporidium, *E. coli* 0157, some resistant organisms including penicillin-resistant pneumococcus, frankly and intermediate penicillin-resistant pneumococcus, group A streptococcus, vancomycin-resistant enterococcus, and hepatitis C antibody-positive persons. Data will also be collected on dengue, legionella, malaria, and tuberculosis.

The census system will provide numerator data. Beginning in early 1997, the VA also obtained denominator data from a rolling 12-month database typically derived from workload data, such as ICU and hospital days. The data are expected to be of fine quality and to lend themselves readily to statistical analysis, thus permitting the agency, in a more timely fashion than has

previously been the case, to track its interventions and determine whether objectives are being met.

In 1997, the agency will fund an Emerging Pathogen Research Initiative that will support investigator-initiated research. The funding level remains to be determined, but grants are currently coming in and a review process is in place.

Collaborations

VA will be working with DOD on a mutual research agenda.

Budget Allocations

No data.

Future Challenges/Concerns/Issues

- Problems of inconsistency of reporting data at the state level, at least partly owing to the Privacy Act and public laws related to patient privacy required by the agency's oversight group, the U.S. Congress.
- Questions as to whether treatment algorithms provided for certain diseases are, or could be, consistently followed across all 170 VA hospitals and by its thousands of physicians.
- Questions about degree to which VA databases are adequately representative of the total U.S. population.
- Possibilities for VA information base to provide useful data on susceptibilities in its populations to bacterial pathogens in the general population.

WORLD BANK

R&D Priorities

The Bank sees its primary mission as promoting socioeconomic development in low-income countries. It has increasingly come to recognize the critical role of investments in health in that development.

The Bank has recently begun to focus on prospects for integrating capitalization of health product development into its agenda, motivated by a 1995 meeting of the Committee for Health Research and Development at which needs to promote health product development for low-income countries were discussed. The Bank believes the private sector is an essential component in any such endeavor, one so far largely neglected by the public sector.

The Bank is considering a range of options for its involvement and trying to determine what gaps it might fill most usefully. A possible priority is the longstanding need for a malaria vaccine.

Implementation

The Bank is modifying its policy of funding on a country-only basis to offer leeway for activities around generic, cross-cutting issues affecting a number of countries in comparable fashion. This will permit the Bank to act as a corporate entity with a corporate policy in a substantive area, in this case one encompassing health product development. It will be able to play a catalyzing role through corporate statements in support of cross-cutting health product missions (e.g., immunization).

After much consideration, the Bank has decided to focus initial activity on pharmaceuticals and vaccines, with possible later attention to development of diagnostics.

With the Rockefeller Foundation, the Bank is working to promote public-/private-sector collaboration in health product development for low-income countries. The first step was to survey high-level representatives from the pharmaceutical industry to determine what industry is and is not doing regarding infectious diseases, and to identify barriers to private-sector involvement. The survey and later discussions yielded concrete suggestions on what the public sector might do to encourage such involvement.[*]

[*] These suggestions coincided with many ideas that emerged in the Forum workshop and are reflected in the Summary of this report and the associated table (Table 2).

Collaborations

The World Bank/Rockefeller Initiative, as above.

Through its Country Assistance Strategy, the Bank can motivate attention at the country level to catalyze greater activity in areas it sees as high priority. The Bank has discussed with the Department of State the possibility of designating infectious diseases as one of those areas. The two institutions are also discussing the potential of the Bank's new policy flexibility and support for developing products for meningitis and malaria.

The Bank also co-sponsors the International AIDS Vaccine Initiative (IAVI), a fulcrum for multisectoral collaboration on a specific technology for a specific disease.

Budget Allocations

No data.

Future Challenges/Concerns/Issues

- The Bank is seeking commitments from industrial firms to take a lead in selected initiatives. At such time as a given industry expresses genuine interest, the Bank will embark on a preliminary design stage focused on two to three products to which value can be added, and/or provide support for products approaching testing in particular markets.
- The main issues emerging from the Bank's pharmaceutical industry survey were:

— Lack of adequate information on research under way in universities, research councils, and biotechnology companies worldwide; for example, on receptors, enzymes, and compounds industry could screen to generate more product leads.
— The need to reduce costs and duration of clinical trials without compromising safety and efficacy.
— The need to increase market potential of products primarily for diseases in developing countries.

APPENDIX B

Workshop Agenda

NATIONAL ACADEMY OF SCIENCES INSTITUTE OF MEDICINE

FORUM ON EMERGING INFECTIONS

2nd Meeting: 10–11 February 1997

Monday, February 10th

9:30 MEETING BEGINS

ELEMENT 1: THE EMERGING INFECTIOUS DISEASE R&D AGENDA AND INDUSTRY'S RESPONSE

1. What are the public-sector health agendas, priorities, *and/or* particular concerns in connection with R&D related to emerging infectious diseases?

2. What components of these are shared and which are specific to individual public-sector entities?

Thumbnail Reports—Priorities/Relevant Activities:

John LaMontagne (NIAID)

James Hughes/Joseph McDade (CDC)

Michael Hughes (VA)

Stephen Morse (DARPA)

Nancy Carter-Foster (State)

Veerle Coignez Sterling (World Bank)

3. In which of the areas indicated in the public health agenda and priorities list is industry already working, who is doing so, and what are they doing?

Overview:

John Siegfried (PhRMA)

Additional Comments:

Individual industry representatives who are members of the Forum

4. Where are the gaps between what the public sector needs and what industry is already doing?

Gap Analysis and Discussion

1:30 RECONVENE

ELEMENT 2: A LEARNING CASE—THE CHILDREN'S VACCINE INITIATIVE

5. What have we learned? *(NOTE: While particular topics are indicated for some individuals, all are highly knowledgeable about this activity and can speak to a range of relevant points.)*

Panel Presentation and Discussion—Attempts to Modify the Structure of Incentives for Industry to Produce "Social Products": The Illuminating Case of the Children's Vaccine Initiative

William Hausdorff (Wyeth-Lederle)

Pamela Johnson (United Nations)

Amie Batson (Vaccine Supply and Quality Unit, WHO Global Programme for Vaccines and Immunization)

William Muraskin (Department of History, Queens College)

Jack Melling (Salk Institute, Swiftwater)

Roy Widdus (WHO/Children's Vaccine Initiative)

Patents: Protection and Problems

Charles Caruso (Merck and Company, Inc.)

ELEMENT 3: OTHER MODELS AND MECHANISMS

Special Disease-Focused Initiatives:

Malaria Vaccine Development Board

Phillip Russell (Johns Hopkins School of Hygiene and Public Health)

International AIDS Vaccine Initiative (IAVI)

Seth Berkley (Rockefeller Foundation)

Legislative Mechanisms

Orphan Drug Act

Anne Marie Finley (Committee on Government Reform and Oversight, Subcommittee on Human Resources, U.S. House of Representatives)

6. Contemplating what we have heard today, what do we think we know about what works and what does not, and what would be the most useful things that could/should happen next?

GENERAL DISCUSSION and CHAIRMAN'S SUMMARY

5:30 ADJOURN

Tuesday, February 11th

8:30 MEETING RESUMES

ELEMENT 4: Discussion Panel, FDA and Industry Representatives

7. Current Legal/Regulatory Issues Around Development of Drugs and Vaccines for Emerging Infections

- **Antimicrobial Resistance and Labeling**
- **Combination Products: Vaccines and Pharmaceuticals**
- **Special Mechanisms to Expedite Approval (e.g., fast-track mechanisms)**
- **Use of Foreign Data/ICH Activities**
- **Product Availability**

From the Food and Drug Administration:

Elaine Esber

Mark Goldberger

Jeffrey Murray

Stuart Nightingale

From the Forum on Emerging Infections: Member Representatives from Industry

10:30 ADJOURN

APPENDIX C

Public-/Private-Sector Collaboration in Pharmaceutical Research and Development: Inventory of Mechanisms

Gretchen Kidder and Christina Thacker
Staff, Institute of Medicine

LEGISLATIVE AND REGULATORY MECHANISMS

Bayh-Dole Act

Background

In 1980, the Patents and Trademarks Law Amendment (PL 96-517), also known as the Bayh-Dole Act, was enacted in an effort to promote the commercialization of government-funded inventions. The statute provides that non-profit and small-business recipients of government grants, contracts, or cooperative agreements are allowed to retain title to the inventions made with that support, provided that they comply with the act's procedural requirements and take steps to achieve practical application of the inventions. With relatively few restrictions, recipients of federal funding may commercialize such inventions themselves or license them to others for commercialization (Sherman and Englund, 1995).

Outcomes

Bayh-Dole has been credited with increasing both the number of university patents and the number of licenses to industry. The amount of money provided to universities from private industry has also increased, as have payments in royalties to universities. Bayh-Dole is also thought to have had positive economic impact, including an estimated $20 billion in earnings from all stages of early and late development of new products, support for an estimated 150,000 jobs annually, and increased tax revenues of $3.9 billion (Terry, 1996). The act is also considered responsible for accelerating the development of the entire biotechnology industry (Schimmel, 1996).

Issues

Nonetheless, the new partnerships between industry and academia have had some rocky patches and increasingly difficult interactions. Some of the conflict

is thought to arise from divergent attitudes regarding intellectual property rights and patent policy (Sederoff and Sederoff, 1996). The academic tradition of publishing research results is incompatible with industry's proprietary and competitive concerns.

Another, related area of tension has to do with the experimental-use exemption provided for under the act, which is intended to foster freer use of patented biotechnology for non-profit research by academic institutions. Industry is resistant to the exemption, a position some analysts feel will be prejudicial to university-based science (Sederoff and Sederoff, 1996).

Yet another issue has to do with overhead costs. Bayh-Dole stipulated that an industry entering into partnership with an academic institution would cover overhead costs. Recently, however, industry concerns with cost cutting have generated some unwillingness to pay all overhead costs (Terry, 1996). There are also many issues surrounding the appropriate allocation of funds that require clarification.

All these issues suggest that there is a need for further refinement of guidelines for collaborative agreements of the sort contemplated under the act (Schimmel, 1996).

References

Schimmel P. A two-way street between the university and the biotechnology enterprise. *Journal of NIH Research* 8(8):41-43, 1996.

Sederoff R, and M Sederoff. Taq polymerase and the experimental-use exemption. *Journal of NIH Research* 8(8):43-44, 1996.

Sherman C, and S Englund. When the feds share the tab. *Legal Times,* 15 May 1995. (Lexis-Nexis, Allnews, Bayh-Dole).

Terry WD. The academic-industrial complex: Doing well and doing good. *Journal of NIH Research* 8(8): 39, 1996.

Orphan Drug Act

Background

In 1983 Congress amended the federal Food, Drug, and Cosmetics Act with the Orphan Drug Act (ODA/PL 97-414). The ODA was created to provide incentives for companies to develop therapies that otherwise would not be commercially viable because they are needed only by a relatively small number of patients. The act was intended to prompt the pharmaceutical industry to develop drugs for use against rare diseases affecting fewer than 200,000 people in the United States. The incentives for industry include research grants, a 50-percent income-tax credit on most clinical research expenditures, assistance with FDA approval, and exclusive license to market the product for 7 years immediately

following FDA approval. This 7-year exclusivity has emerged as the most powerful of these incentives for industry (IOM, 1993).

Outcomes

Since inception of the ODA, 130 orphan drugs have been approved for marketing. With the United States experiencing benefits from this legislation, Japan and Singapore have enacted similar laws and the European Union is following suit (Meyer, 1996). In the 17 years prior to the act, industry sponsored 34 marketed and 24 experimental orphan drugs; in the first 7 years since it was passed, it sponsored 39 of 42 marketed orphan products (Ashbury, 1991).

In recent years, although a bill has been introduced repeatedly in the Senate to extend the orphan drug tax credit permanently, it has not been passed. According to Senator Orrin Hatch (R-UT), sponsor of the bill introduced in February 1997, since 1983 100 drugs have been approved and some 600 are now in development (Washington Fax, 1997). The bill was referred to the Senate Committee on Finance in February and as of the date of publication no further action has been taken.

Issues

There are concerns that many orphan drugs, developed with considerable assistance from the U.S. government, have earned unexpectedly high profits for the manufacturers. A major flaw in the original regulation is that it provides no authority for the government to pressure for lower prices. In 1990 this concern prompted Congress to approve a measure that would tighten the requirements under which orphan drug status was applicable. The provisions included removing orphan drug status if the patient population exceeds 200,000 and allowing more than one manufacturer to market an orphan drug if simultaneous development occurred (Office of Technology Assessment [OTA], 1991). High prices and high volume sales have created the dilemma for lawmakers of how to stimulate development without causing price increases that make drugs inaccessible. In an attempt to limit high profits, legislative proposals in recent years have included decreasing the market exclusivity provision to only 4 years, with the possibility for a 3-year extension upon proof of "limited commercial potential" (Health Legislation and Regulation, 1994). Some suggestions have included withdrawal of market exclusivity once sales reach a specified amount.

The research and development tax credit remains a recurring issue that has only been temporarily extended, year after year. A proposed measure to permit the tax credit to be applied to past or future tax liability might eliminate discrimination against small biotechnology companies in the development stage. If the tax credit were made permanent, companies may be better enabled to commit to the lengthy

and burdensome process of developing orphan products (*Marketletter,* 1995). A requirement of the tax credit could be to invest the credit in orphan drug research.

References

Ashbury CH. The Orphan Drug Act: The first seven years. *Journal of the American Medical Association* 265(7):893-897, 1991.

Institute of Medicine (IOM). *The Children's Vaccine Initiative: Achieving the Vision.* VS Mitchell, NM Philipose, and JP Sanford, eds. Washington, D.C.: National Academy Press. 1993.

Marketletter. Extension of R&D Tax Credits Sought. (Nexis. IAC (SM) Newsletter Database. Information Access Company: Marketletter Publications Ltd.) 1995.

Meyer AS. Testimony before the Committee on Government Reform and Oversight, U.S. House of Representatives, 12 September 1996.

Office of Technology Assessment, U.S. Congress. *Biotechnology in a Global Economy* (OTA-BA-494). Washington, D.C.: U.S. Government Printing Office. 1991.

Orphan Drug Revisions Moving Again. Health Legislation and Regulation. (Nexis. IAC (SM) Newsletter Database. Information Access Company: Faulkner & Gray, Inc.) 1994.

Washington Fax, Life Science. B Metheny, ed. Senate bill would extend permanently the orphan drug tax credit. 24 February 1997.

National Vaccine Injury Compensation Program

Background

Concerns about the costs of liability litigation motivated many pharmaceutical companies to drop out of vaccine manufacturing in the 1970s and early 1980s (IOM, 1985, 1993). Large and unpredictable settlements were determined to be an unreasonable risk, given the relatively low profit margins associated with vaccines. As a result, several expert committees endorsed the creation of a no-fault compensation program and, in 1984, the American Academy of Pediatrics took the initiative in seeking federal legislation to create what is now known as the National Vaccine Injury Compensation Program (NVICP). The National Childhood Vaccine Injury Act, enacted in 1986, created NVICP, which was implemented in 1988. The program was an attempt both to compensate the families of children adversely affected by government-mandated vaccines and to shore up the vaccine industry by attenuating liability risk through the imposition of a vaccine excise tax, to be paid into a dedicated trust fund (Public Health Service Act, 1987; 100 Stat. 3756, codified as Title XXI of the Public Health Service Act at 42 USC 300aa-1 *et seq.* [Supp. V

1987]; the Compensation Program is codified as Subtitle 2 of Title XXI, 42 USC 300aa-34). The excise tax was removed by the Secretary of the Treasury on January 1, 1993, when a bill unrelated to the NVICP but containing language that would have extended the tax, was vetoed by President Bush. The trust fund had a balance of about $620 million at the beginning of 1993.

The NVICP was intended as an alternative, rather than exclusive, source of compensation. Petitioners were allowed to reject a given decision and request review of the case by the U.S. Claims Court; if not satisfied with the review, petitioners could appeal to the U.S. Court of Appeals. In order to be an effective alternative form of compensation, the NVICP was designed to work quickly and not involve itself with causation, one of the most costly and time-consuming components of tort action for personal injury (IOM, 1996).

Outcomes

As of 1993, there appeared to have been a drop in the number of vaccine-related lawsuits and increased activity in vaccine-related research and development (IOM, 1993). However, at the time, none of the companies that had dropped out of vaccine manufacturing in the 1970s and 1980s had returned, a situation that has since changed (Mercer Management Consulting, 1994). More recently, several foreign companies have expressed interest in the U.S. vaccine market, either by applying for Food and Drug Administration (FDA) licenses for their products or by creating alliances with companies and entities that currently hold U.S. product licenses (IOM, 1996).

Issues

In 1993, one analyst noted that the number of "retrospective cases" (for vaccinations prior to October 1, 1988) had been so voluminous that there were widespread doubts as to whether the funding levels were adequate to sustain the program (Garber, 1993). By August 1996, however, the Department of Health and Human Services (DHHS) had fully adjudicated over 75 percent of the pre-1988 claims backlog (Health Resources and Services Administration [HRSA], 1996).

References

Day K. Vaccine maker gets a shot in the arm. *Washington Post*, 11 March 1996.

Garber S. *Product Liability and the Economics of Pharmaceuticals and Medical Devices* . Santa Barbara, CA: Rand Corporation, Institute for Civil Justice. 1993.

Health Resources and Services Administration (HRSA). National Vaccine Injury Compensation Program: Summary of current issues. [online] http://www.hrsa.dhhs.gov/bhpr/vicp/sumcur.htm. 1996.

IOM. *Vaccine Supply and Innovation*. Washington D.C.: National Academy Press. 1985.

IOM. *The Children's Vaccine Initiative: Achieving the Vision*. VS Mitchell, NM Philipose, and JP Sanford, eds. Washington, D.C.: National Academy Press. 1993.

IOM. *Contraceptive Research and Development: Looking to the Future* . PF Harrison, and A Rosenfield, eds. Washington, D.C.: National Academy Press. 1996.

Mercer Management Consulting. *Summary of UNICEF Study: A Commercial Perspective on Vaccine Supply*. New York: Mercer Management Consulting. 1994.

Cooperative Research and Development Agreements

Background

Cooperative Research and Development Agreements (CRADAs) are authorized under the Federal Technology Transfer Act (FTTA) of 1986 (PL 99-602). CRADAs allow the transfer of technology, knowledge, and expertise from government laboratories to the private sector for further development and commercialization. Under a CRADA, federal laboratories and private sector companies conduct research jointly and the collaborating company acquires patent rights at the outset of the collaboration. The FTTA provides for the sharing of royalties with government inventors from the licensing of products developed under CRADAs and from inventions made through an agency's intramural research programs (OTA, 1991). Under CRADAs, the government can offer the option of obtaining an exclusive license for inventions created in the course of research conducted under the agreement. "This provides incentives for companies to enter into collaborations that will expedite the commercialization of government inventions for the benefit of the public" (Fauci, 1996).

Outcomes

As of 1991, the National Institutes of Health (NIH) had roughly 150 CRADAs in effect and an additional 100 in various stages of negotiation (OTA, 1991). Currently, more than 2,000 CRADAs have been signed (Schacht, 1996). CRADAs have facilitated the discovery and development of a number of new drugs including taxol, didanosine (ddl), dideoxycytidine (ddc), trimetrexate, and fludarabine (IOM, 1994).

Issues

Consumer representatives and members of the U.S. Congress have criticized the private commercialization of government-sponsored inventions, arguing that the government should exercise control over the price of drugs the development of which has been supported by federal funds. This argument encouraged NIH to adopt a policy of adding a "reasonable pricing" clause into CRADAs, a matter which, together with the subject of drug pricing in general, remains hotly debated and politically controversial (IOM, 1994). "As the 104th Congress determines its science and technology policies, the role of the CRADAs may be debated within the context of initial indications of Republican preferences for government support of basic research and measures which do not involve direct federal funding for private sector technology development" (Schacht, 1996).

Another related issue is that the CRADA process has been slow. Legislation has been introduced by Representative Morella (R-MD) and Senator Rockefeller (D-WV) that would revise the FTTA to include a requirement for automatic assignment of intellectual property rights to CRADA partners. This would expedite the CRADA approval process by guaranteeing industry partners exclusive field-of-use licenses (Allen, 1997).

References

Allen J. GOGO and GOCO Tech Transfer Policies. [Online] (http://www.nttc.edu/aftte/goco.html) 1997.

Fauci A. Biomedical research in an era of unlimited aspirations and limited resources (Country profile, United States of America). *Lancet* 348 (9033):1002–1003, 1996.

IOM. Government and Industry Collaboration in AIDS Drug Development (Workshop Summary). Washington, D.C.: National Academy Press. 1994.

Office of Technology Assessment, U.S. Congress. *Biotechnology in a Global Economy* (OTA-BA-494). Washington, D.C.: U.S. Government Printing Office. 1991.

Schacht W. Cooperative Research and Development Agreements. Congressional Research Report, Penny Hill Press. 1 May 1996. (Lexis-Nexis, allnws, CRADAs).

Small Business Innovation Research Program

Background

The Small Business Innovation Research Program (SBIR) was enacted in 1982 as part of the Small Business Innovation Development Act (PL 97-219), which required the agencies of the Public Health Service and certain other

federal agencies to reserve a specified amount of their research and development budget for SBIR programs. The program seeks to stimulate technological innovation, use small businesses to meet federal R&D needs, and increase private sector commercialization of innovations derived from federal research and development. The primary award mechanism to small businesses is a grant, but award mechanisms also include cooperative agreements or contracts.

To be eligible for the SBIR program, a firm must qualify as a "small business concern" according to 13 CFR, Part 121. For qualification, a firm must be for-profit, independently owned and operated, not dominant in the field of operation in which it is proposing, have its principal place of business in the United States, be at least 51 percent owned by U.S. citizens or lawful permanent residents, and not employ over 500 people (Department of Health and Human Services [DHHS], 1993). Restrictions on rights to data developed under SBIR grants include a royalty-free license on all patent rights to the U.S. government for federal use. The government also reserves the right to require the patent holder to license rights in certain circumstances; otherwise, rights to data generally remain with the award recipient. The recipient may copyright and publish material developed under SBIR grants.

Outcomes

For the 1997 fiscal year, agencies with extramural research and development budgets over $100 million must reserve 2.5 percent thereof for SBIR grants under the terms of the program's authorization (*Washington Fax*, 29 January 1997). According to NIH officials, SBIR has been difficult to administer because much of its regulation comes from outside the jurisdiction of its government-wide funding agencies. Since the program was created by Congress, and is administered by the Small Business Administration (SBA), changes must be approved by the Small Business Committee.

Issues

At a recent conference held to assess the program, NIH presented examples of successful collaborations and participants expressed some of their frustrations. Comments centered on the quality of applications and reviews and general communication problems.

The general perception is that applications submitted for SBIR grants are not of comparable quality with projects funded through other NIH extramural research funding mechanisms. To counter this perception NIH has been granted latitude to move SBIR projects around among institutes in order to fund only the best applications. The review process, lasting approximately 6 months, includes a peer review panel composed primarily of non-federal scientists reviewing for

scientific and technical merit; applications are then reviewed by the National Advisory Council or Board of the awarding agency.

Concerns regarding the review process focus on the various components of the application. Applications contain a commercialization portion as well as a research portion and, although review panels include representatives from small businesses, neither they, nor the scientists, may have a thorough understanding of commercial language or issues.

This provided a window to a much larger, general concern, that of improving communications among applicants, academic scientists, and NIH administrators throughout the entire process. Many applicants have experienced a lack of enthusiasm about the program from several NIH institutes, centers, and divisions. The American Society for Cell Biology and the Joint Steering Committee for Public Policy have suggested assembling a committee to develop recommended guidelines. Others at the conference suggested some vehicle for ongoing communication about administrative problems for all who have a stake in the process outcome (*Washington Fax*, 29 January 1997).

References

Health Resources Services Administration (HRSA). Omnibus Solicitation of the Public Health Service for Small Business Innovation Research (SBIR) Grant and Cooperative Agreement Applications. Washington, D.C.: Department of Health and Human Services. 1993.

IOM. *The Children's Vaccine Initiative: Achieving the Vision*. VS Mitchell, NM Philipose, and JP Sanford, eds. Washington, D.C.: National Academy Press. 1993.

Washington Fax, Life Science. B Metheny, ed. Meeting on Small Business Innovation Research program disappoints. 28 January 1997.

Washington Fax, Life Science. B Metheny, ed. Conference attendees voice problems with Small Business Research grants. 29 January 1997.

Small Business Technology Transfer

Background

The Small Business Research and Development Enhancement Act of 1992 established the Small Business Technology Transfer Program (STTR) as a three-year pilot, modeled after the Small Business Innovation Research Program (SBIR). STTR activities began in FY94 and, as of September 1997, the program had been reauthorized by the U.S. House of Representatives to continue through FY 2000. Its purpose is to provide strong incentives for small companies and researchers at non-profit research institutions, contractor-operated federally-funded R&D centers, and universities, to work as a team to move ideas from the research phases

into the marketplace. The program is competitive and proposals must be developed and executed cooperatively. Unlike SBIR, all STTR projects must include a research institution, which can provide up to 60 percent of the work. Under STTR's distinctive partnering concept, research can be initiated either by scientists in a small business or in a research institution.

STTR grants, contracts, and agreements are divided into three phases. In Phase I, recipients conduct research to determine an idea's feasibility and merit. In Phase II, promising Phase I ideas are further developed. Phase III is the commercial or agency application of the idea. STTR funds the first and second phases; private or non-STTR funds are used for the third phase. The program is funded by a 0.15 percent set-aside from research agencies spending over $1 billion on research and development. Five agencies presently contribute to STTR: Department of Energy, Department of Defense, National Science Foundation, National Aeronautics and Space Agency, and National Institutes of Health.

Outcomes

In the first three years of the program, STTR awarded 784 grants totaling $115 million. The program is credited with increasing researcher productivity and decreasing costs in specific research areas; even projects that have not achieved commercialization have contributed to the base of scientific knowledge. A 1996 GAO report found participating agencies to be pleased with the proposals received.

References

Washington Fax, Life Sciences. B Metheny, ed. House passes small business technology transfer bill. 22 September 1997.

Small Business Technology Transfer (STTR) [Online] (http://dticam.dtic.mil/sttr/sttr.html) 1997.

Intellectual Property Rights/Patent Protection

Background

United States The primary goal of the United States patent system is to advance technological and economic development by stimulating innovation and investment. Once awarded, patent protection offers a 17-year right to exclude others from making, using, or selling the invention throughout the United States (35 USC 154), thus offering an incentive for inventors to invest time and money in research and development. The pharmaceutical industry enjoys a further benefit: When a patent claims that a human drug product has

undergone regulatory review to be commercialized or marketed, it may be eligible for an extension of up to 5 years (OTA, 1991). Although a patent gives the inventor the right to exclude others from making, using, or selling the invention for 17 years, it does not grant the inventor any affirmative right to make or use an invention. Commercial use of a patented invention can be regulated by federal, state, or local law (OTA, 1991).

The Bayh-Dole Act of 1980 lessened restrictions for non-profit institutions, including universities, to obtain patents and award exclusive licenses on government-supported research. (See also Bayh-Dole Act.) The Federal Technology Transfer Act of 1986 made it possible for private companies to obtain exclusive licenses on work done by government scientists. The Drug Price Competition and Patent Term Restoration Act of 1984 (PL 98-417) was enacted to restore part of the patent life lost during the regulatory approval process; it allows the extension of the patent term equal to the total time taken by the FDA to review the new drug application plus one-half of the clinical testing time, but not beyond 14 years of effective patent life (IOM, 1993). The act also modified the abbreviated new drug application process to make FDA approval possible for companies to market generic versions of drugs approved by the FDA since 1962 (IOM, 1993).

International Most countries have inadequate systems of intellectual property rights protection. For U.S. companies, such limited protection does not create an incentive to invest in these countries or transfer particular types of technology (National Research Council [NRC], 1993). In contrast to the United States, in the international arena most countries require a patent owner to use or license a patented invention within a specified time period. A few international agreements do exist, providing limited protection for U.S. companies conducting business abroad. The Paris Convention for the Protection of Industrial Property provides two basic rights: 1) the principle of national treatment that allows nationals of any signatory nation to enjoy the advantages that each nation's laws grant to its own nationals in all other countries of the union, and 2) the right of priority that enables member country nationals to first file a patent application in any member country and, thereafter, to file an application for the same invention in any other member country within 12 months and receive the benefit of the original filing date (OTA, 1991). Subsequent agreements, including the Patent Cooperation Treaty and the Budapest Treaty, have sought to increase global harmonization of patenting procedures.

Outcomes

Legislative efforts to provide incentives have resulted in the negotiation of cooperative research and development agreements (CRADA) with private industry (*Lancet*, 1993). Although successful, a continuing problem has been

the pharmaceutical industry's rejection of government requests for more reasonable pricing in negotiating CRADAS, the pharmaceutical companies maintaining that high prices are often justified by the value they add in manufacturing the final product (*Lancet*, 1993). (See also CRADAS.)

Issues

Despite a generally favorable climate, a number of elements affect U.S. competitiveness in the protection of intellectual property. The patent application backlog at the Patent and Trademark Office, uncertainties in the United States and internationally regarding what constitutes patentable subject matter, procedural distinctions in U.S. law (e.g., first-to-invent versus first-to-file, grace period, secrecy of patent applications, and deposit considerations), uncertainties in interpreting process patent protection, and patent infringement litigation—all constitute unsettled areas that could affect incentives for developing new inventions (OTA, 1991). Controversy surrounds basic disagreements or assertions that patents inhibit or encourage the development of new products (*Lancet*, 1993). Since the main source of motivation for researchers is often the opportunity to publish their results, patent protections generally benefit the company or institution as a whole rather than the individual innovator (NRC, 1993).

Two types of patent protection exist for pharmaceuticals: process patents and product patents. Process protection is favored by many developing countries, but it is often worthless to pharmaceutical companies because the burden of proof for infringements is too difficult, making legal action impractical. As a result, pirate companies in these countries freely produce copies of innovative drugs, and some export them to other markets (Peck, 1989). To counter such injustices, and as a means to improve trade and provide more effective protection of intellectual property in a global marketplace, some argue for further harmonization of intellectual property law (OTA, 1991). Yet this is not a universally held belief; much uncertainty surrounds the assessment that trade would be improved and more effective protection would result from such an agreement (NRC, 1993).

Another issue in developing a new international intellectual property rights agreement is the filing system for applications. Most countries besides the United States award patent rights based on the earliest application filed for a certain invention. United States patent law requires establishment of evidence proving the earliest date the invention was conceived. Many countries will not consider a treaty unless the United States agrees to a "first-to-file" system (IOM, 1993). Such a system would allow for earlier disclosure of invention details; improve protections for U.S. companies and their products abroad; and entail fewer resources now used to determine who invented a product first.

References

IOM. *The Children's Vaccine Initiative: Achieving the Vision*. VS Mitchell, NM Philipose, and JP Sanford, eds. Washington, D.C.: National Academy Press. 1993.

Lancet. Editorial: The patent craze and academia. 342 (8885):1435–1437, 1993.

National Research Council (NRC). *Global Dimensions of Intellectual Property Rights in Science and Technology*. Washington, D.C.: National Academy Press. 1993.

Office of Technology Assessment, U.S. Congress. *Biotechnology in a Global Economy* (OTA-BA-494). Washington, D.C.: U.S. Government Printing Office. 1991.

Peck JC, and KH Rabin. *Regulating Change: The Regulation of Food, Drugs, Medical Devices and Cosmetics in the 1990s*. Food and Drug Law Institute. 1989.

Product Liability Protection

Background

The objectives of product liability rules are to compensate individuals injured by unreasonably dangerous products, to deter the marketing of dangerous or defective products, and to resolve disputes between those injured and manufacturers (Smith, 1996; IOM, 1996). Since no federal product liability law exists in the United States, state statutes and common law govern liability issues. Companies therefore tend to rely on FDA regulations in asserting compliance and seeking a defense against allegations in product liability suits. Yet, courts have generally ruled that FDA regulations define minimum standards, affording only moderate protection for companies. Additionally, failure to comply with regulations is often taken as evidence of negligence. A company that ignores a safety problem suggested by clinical trials or fails to report it to the FDA in its application for marketing, could later discover serious liability problems. Although the current system encourages compliance with regulations and even encourages companies to go beyond those standards, it offers little protection (Garber, 1993).

Outcomes

Because of liability risks, the withdrawal of a company from a particular pharmaceutical market reduces competition, which consequently may lead to increased prices (Garber, 1993). Smaller companies may have advantages over larger ones in coping with liability since they are less attractive targets, have less to lose, and have fewer other products that could be affected (Garber, 1993).

Although a lack of availability is often cited as a result of potential liability,

some companies, expecting significant profit potential, do take such risks. An example is companies producing oral contraceptives, which are a high-volume, profitable market; in other words, the profit potential outweighs the cost and liability risks (IOM, 1993).

Issues

Generally, liability poses a significant threat to profits. Pharmaceutical companies market products with the knowledge that they may eventually be sued; most firms accept this risk, adjusting prices upward. Direct costs of claims (i.e., costs of defense, settlements, and awards), decreasing sales, and hence profits, as well as the indirect costs from information or negative publicity generated by lawsuits, contribute to the risks and associated costs that are often passed to the patient (IOM, 1985). Perceived liability potential can affect behavior in the absence of actual liability cost, but one analyst finds little evidence that liability is discouraging drug innovation involving biotechnology (Garber, 1993). In order to have some compensation, an IOM Committee to Review the Fialuridine (FIAU) Clinical Trials recommended the establishment of a system of no-fault compensation for research injury by government, sponsors, or some combination of both (IOM, 1995).

Another suggestion to protect manufacturers, a "regulatory standards" defense, would allow defendants to assert that compliance with FDA requirements shelters them, in varying degrees, from liability (Bartlett Foote, 1996). Such a defense would not hold a manufacturer or seller of a drug liable under any of the relevant legal theories (i.e., misrepresentation, warranty, negligence, or strict liability), assuming that the drug was in compliance with all applicable requirements of United States federal food and drug law at the time that drug was made or sold, for any injury related to design, or for failure to provide adequate warning or instruction regarding any danger associated with its use, nor would a company be held liable if the FDA had not asserted that the drug was not in compliance (IOM, 1996).

References

Bartlett Foote S. Review of *Bendectin and Birth Defects: The Challenges of Mass Toxic Substances Litigation*, by MD Green. *Science* 273:196, 1996.

Garber S. *Product Liability and the Economics of Pharmaceuticals and Medical Devices*. Santa Monica, CA: Institute for Civil Justice, Rand Corporation. 1993.

IOM. *Vaccine Supply and Innovation*. Washington, D.C.: National Academy Press. 1985.

IOM. *The Children's Vaccine Initiative: Achieving the Vision*. VS Mitchell, NM Philipose, and JP Sanford, eds. Washington, D.C.: National Academy Press. 1993.

IOM. *Review of Fialuridine (FIAU) Clinical Trials*. Washington, D.C.: National Academy Press. 1995.

IOM. *Contraceptive Research and Development: Looking to the Future* . PF Harrison, and A Rosenfield, eds. Washington, D.C.: National Academy Press. 1996.

Smith SD. The critics and the "crisis": A reassessment of current conceptions of tort law. *Cornell Law Review* 72:765–798, 1987, In *Contraceptive Research and Development: Looking to the Future*. PF Harrison, and A Rosenfield, eds. Washington, D.C.: National Academy Press. 1996.

NIH Legislative Proposal for Product Liability Exemption for Public Health Service IND and IDE Research

Background

Although a product liability exemption for manufacturers of vaccines exists, the lack of liability protection for manufacturers led the NIH in 1995 to propose legislation exempting research institutions, investigators, and manufacturers from claims for non-negligent injury occurring in PHS-funded studies of new drugs or devices under an FDA-approved investigational new drug or device (IND or IDE). Such drugs or devices have gone through extensive testing requirements, the subject has been informed that there may be unknown risks, and the drug or device has been made as safe as the current state of scientific knowledge is able to make it. Because the only available recourse for injured research subjects is through the courts, NIH also proposed compensation through the Federal Employees' Compensation Act (FECA).

Issues

Because of unavailable or prohibitively expensive product liability insurance, research often is impeded or not conducted. Small businesses have been unable to proceed with clinical testing of devices developed in the Small Business Innovation Research Program (SBIR) program owing to the inability to obtain product liability insurance. The lack of protection remains a major obstacle despite evidence that appropriate safety measures have been taken and federal regulations followed, that is, assurances of appropriate protections for human subjects have been attested to by an Institutional Review Board, PHS staff, and the dual-level peer review bodies, and all animal testing required by the FDA before granting clearance for human testing has been completed.

The other side of the liability protection issue concerns compensation. Although the federal government provides for a program of no-fault compensation for certain individuals who have been injured by vaccines under the PHS Act, the PHS proposal recommends compensation for PHS IND and IDE research through FECA. PHS has recommended broadening the definition of "federal employee" for purposes of eligibility for benefits distributed under FECA, to include human subjects of non-therapeutic research procedures conducted or supported by HHS and to provide no-fault medical treatment and/or other compensation distributed under the FDA, in the event of research-related injury.

References

Gaines, George W. National Institutes of Health Fiscal Year 1997 Legislative Proposal: Product Liability Exemption for PHS IND and IDE Research. National Institute of Child Health and Human Development, National Institutes of Health. June 6, 1995.

Prescription Drug User Fee Act

Background

Enacted in 1992, the Prescription Drug User Fee Act authorizes the FDA to charge user fees to prescription drug and biologic drug industries for review of new drug applications or product license applications. The statute does not apply to generic drugs, investigational drugs, or other FDA-regulated products like medical devices or foods. Related fees include charges estimated at $233,000 in 1997 for human drug applications that contain clinical data (other than bioavailability or bioequivalence studies). Prescription drug establishment fees and prescription drug product fees have been phased in from 1993 to 1997. Exceptions generally have been applied toward review of orphan drugs and similar situations (Nightingale, 1992).

Outcomes

Average review times for new drugs seem to have dropped substantially since user fee requirements came into play, although the time prior to acceptance of a new filing has increased (IOM, 1996). The FDA's Annual Report to Congress for fiscal year 1994 revealed that the agency had approved 93 percent of all drugs within a year of a company's application, surpassing the 55 percent benchmark mandated by the Prescription Drug User Fee Act (IOM, 1996).

References

IOM. *Contraceptive Research and Development: Looking to the Future* . PF Harrison, and A Rosenfield, eds. Washington, D.C.: National Academy Press. 1996.

Nightingale SL. From the Food and Drug Administration. *Journal of the American Medical Association* 268(24):3418, 1992.

Drug Approval Process Alternatives: Treatment Investigational New Drugs

Background

Since the mid-1970s, the FDA has approved treatments for individual patients whose life-threatening conditions prove unresponsive to existing therapies, namely through informal "compassionate use investigational new drugs (INDs)" (Shulman and Raiford, 1990). INDs may receive FDA approval once a new drug application (NDA) has been submitted, initiating a process that can take up to 5 years for clinical trials to be conducted before final approval is granted. Treatment INDs were created to supplement the IND/NDA procedure. The first class of drugs to arouse interest in treatment protocols was the cardioselective beta-blockers; several thousand patients with bronchospastic lung disease received the drug metoprolol outside of controlled trials, before the drug was approved in 1976 (Young et al., 1988). Such treatment usage is available once the FDA concludes that evidence of effectiveness and a reasonable assurance of safety exist (Miller Jones, 1989).

In 1987 regulations were published specifying criteria that must be met for treatment use of INDs to be approved. These regulations enable physicians to use INDs for patients who have serious or immediately life-threatening diseases and who are not enrolled in a clinical trial, *if* no comparable or satisfactory alternative drug or therapy is available. This alternative applies only to drugs already in controlled clinical trials. Another of the criteria, to protect firms seeking expeditious development and marketing of promising new therapies, requires the sponsor of a controlled clinical trial to actively pursue marketing approval of the IND with due diligence (Shulman and Raiford, 1990).

Outcomes

Although the intent of creating treatment INDs was in part to facilitate the availability of a promising new drug as early as possible, some companies have elected not to use this alternative, and, instead, have chosen to invest resources in the NDA approval process (Miller Jones, 1989).

Issues

Concerns have been raised that clinical trials would be delayed by a decline in patient enrollment, since when patients are presented with a choice, they may opt to obtain the drug through a treatment IND which is less restrictive and eliminates the chance of receiving a placebo or possibly a less effective drug (Shulman and Raiford, 1990). Other areas of concern include developing procedures to identify and evaluate unexpected deaths or serious illnesses resulting from the use of the experimental drugs; deciding who should pay the costs of associated medical care, administering the drugs, and monitoring laboratory procedures; determining the level of liability of sponsoring drug companies or physicians participating in the program; establishing specific criteria for determining patient eligibility; and developing informed consent requirements for participating patients.

References

Miller Jones J. *Paying for Promise: Covering and Reimbursing for Investigational Drugs*. National Health Policy Forum Workshop, Issue Brief No. 545, 5/24/90. Washington, D.C.: George Washington University. 1990.

Nightingale SL, CA Kimbrough, and PH Rheinstein. Access to investigational drugs for treatment purposes. FDA Perspective in *American Family Physician* 50:845-847, 1994.

Shulman SR and Raiford DS. FDA Regulations Provide Broader Access to Unapproved Drugs. Boston: Center for the Study of Drug Development, Tufts University. Reprinted from *Journal of Clinical Pharmacology* 30(7):585-587, 1990.

Young RE, JA Norris, JA Levitt, and SL Nightingale. The FDA's new procedures for the use of investigational drugs in treatment. *Journal of the American Medical Association* 259 (15):2267-2270, 1988.

Drug Approval Process Alternatives: Parallel Tracking

Background

The AIDS epidemic spawned new interest in the question of quicker availability of investigational new drugs (INDs) and, in 1989, Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, supported the initiation of a parallel-tracking system. Its purpose was to make an investigational drug available to desperately ill patients who did not qualify for research protocols but who might benefit from the drug. The idea was to make the drug available "in parallel" to ongoing trials (GWU, 1990).

Outcomes/Issues

The concept of parallel tracking is similar to the treatment IND mechanism. A parallel-tracked drug may be made available even earlier than a drug with treatment IND status. Unlike treatment IND drugs, experimental drugs that have been found to be safe but have not necessarily been conclusively proven effective, would be made available. Many experts believe it may be difficult to know when a drug should be parallel-tracked rather given treatment IND status and some have expressed concern that parallel tracking may discourage patients from entering rigorous clinical trials. Other unresolved issues include developing procedures to identify and evaluate unexpected deaths or serious illnesses resulting from the use of the experimental drugs; deciding who would pay the costs of associated medical care, administering the drugs, and monitoring laboratory procedures; determining the level of liability of sponsoring drug companies or physicians participating in the program; establishing specific criteria for determining patient eligibility; and developing informed consent requirements for participating patients (GWU, 1990).

References

Miller Jones J. *Paying for Promise: Covering and Reimbursing for Investigational Drugs*. National Health Policy Forum Workshop, Issue Brief No. 545, 5/24/90. Washington, D.C.: George Washington University. 1990.

Drug Approval Process Alternatives: Off-Label Use/ Supplemental New Drug Applications

Background

Amendments to the federal Food, Drug, and Cosmetic (FD&C) Act of 1962 mandated that the FDA evaluate the safety and efficacy of all new drugs. The medical conditions against which a given drug is effective and the patient groups for whom the drug has been shown to be effective were to be specified and that information was to appear in the drug labeling. When the FDA approves a drug product, it does so only for the conditions specified on the label; use of a drug for an indication not approved by the FDA is considered an "off-label" use (Jagger, 1996). FDA approval for all new indications requires Phase III clinical trials demonstrating efficacy for such indications (Kennedy, 1996). To initiate this process, a manufacturer must submit a Supplemental New Drug Application (SNDA). Nonetheless, use of drugs for purposes not indicated is common in medicine; a clinician may legally prescribe a drug for an unlabeled use despite the lack of FDA trials to approve the indication involved.

An estimated 80 percent to 100 percent of cancer, pediatric, and rare disease treatment is off-label (Kennedy, 1996).

Outcomes

Third-party payers typically will not pay for drugs that are not specifically approved for the indication being treated. This is said to have been detrimental to patients, particularly those with cancer and rare diseases, who make up a large percentage of those using treatments that are off-label. In 1993, the Omnibus Budget Reconciliation Act (OBRA) required Medicare to consider additional sources beyond FDA approval when determining reimbursement. Reimbursement can now be based on supportive clinical evidence in peer-reviewed publications that have been identified by the Secretary of Health and Human Services or in citations in one or more select medical compendia. (H.R. 3199, currently being considered, proposes a conceptually similar approach with respect to promotion of off-label drug use) (Jagger, 1996). In February 1997, the Secretary of Health and Human Services announced a new public-private plan to provide consumers with easy-to-read labels. Information provided will cover all uses of medications that are approved by the FDA. In addition, physicians and pharmacists will be able to provide information about "off-label" uses customized for each individual patient. This provision provides "useful written information" to patients and will be provided to 75 percent of individuals receiving new prescriptions by the year 2000 and 92 percent by the year 2006 (*U.S. Medicine*, 1997).

Furthermore, the approval time for SNDAs has been criticized as slow and therefore as impeding physician awareness and making it possible for third-party payers to deny payment for therapies, even though they may be considered standard therapy for a given indication, even absent formal clinical trials. The Prescription Drug User Fee Act of 1992 has worked to reduce the amount of time it takes the FDA to approve efficacy supplements by providing the FDA with additional resources and holding it accountable for rapid action on efficacy supplements. Efficacy supplements include not only new indications but new dosage regimes, new routes of administration, new patient groups, and other types of supplements (DiMasi, 1996).

Issues

Another issue is reflected in criticisms that the SNDA process is inefficient. There is sentiment that the FDA gives SNDAs a lower priority than NDAs, a claim that may be reasonable enough given the amount of public and political pressure on the agency to approve new drugs (Meyers, 1996). At the same time, manufacturers are criticized for their reluctance to submit SNDAs even though a drug may, in fact, be widely used for supplemental indications. That reluctance

is largely based on the prohibitive expense of the necessary FDA trials and general lack of incentives to initiate the process. In addition, NIH has been criticized for bias towards funding basic research rather than much-needed clinical research on humans (Meyers, 1996), a bias analyzed and confirmed by federal panels. Lobbying efforts to overcome these biases have resulted from some of these findings (Wurtman and Bettiker, 1995).

Yet another issue is that NIH funding in the area of off-label use has been minimal. In the past, third-party payment to cover subject costs has typically helped to offset costs of large-scale studies of proposed off-label uses. However, Medicare will no longer cover these costs and there are concerns that other third-party payers will follow its lead (Wurtman and Bettiker, 1995). This has placed an undue burden on patients and families who may then find themselves deeply in debt or unable to continue treatment because of excessive costs (Meyers, 1996). A survey of cancer physicians indicated that many altered what they believed to be the best treatment in response to the denial of third-party repayment and 62 percent said they had admitted patients to hospitals as a way to circumvent reimbursement denials (Jagger, 1996).

References

DiMasi J. Written Testimony for the House Subcommittee on Human Resources and Intergovernmental Affairs, Committee on Government Reform and Oversight, U.S. House of Representatives, 12 September 1996.

Jagger S. Prescription Drugs: Implications of Drug Labeling and Off-Label Use . Testimony Before the Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Reform and Oversight, U.S. House of Representatives. U.S. General Accounting Office, 12 September 1996.

Kennedy WJ. Testimony Before the Human Resources and Intergovernmental Affairs Subcommittee, Government Reform and Oversight Committee: PhRMA Statement. 12 September 1996.

Meyers A. "Off-Label" Uses of Pharmaceuticals for Treatment of Orphan Diseases. Testimony Before the Committee on Government Reform and Oversight, Subcommittee on Human Resources and Intergovernmental Relations, U.S. House of Representatives, 12 September 1996.

U.S. Medicine. More prescription information planned. 33(3,4):10, 1997.

Wurtman R, and R Bettiker. The slowing of treatment discovery, 1965-1995. *Nature Medicine* 1 (11):1122-1125, 1995.

FINANCIAL MECHANISMS

Tiered Pricing/Bulk Procurement

Background

Tiered, or differential pricing, is a method of varied pricing of products according to the purchaser and the quantity desired. Bulk procurement of pharmaceutical products has historically permitted a reduced purchase price, notably in the vaccine and contraceptive industries. Tiered pricing is used by the vaccine industry both within the United States and internationally, although U.S. manufacturers have not sold their vaccine products internationally at reduced rates since the early 1980s, with very limited exceptions. In the United States, vaccine companies have customarily sold vaccines to the federal government at discounted prices and to private providers at higher prices, essentially a two-tiered system. Since 1982, manufacturers have been selling pediatric vaccines to the public sector—at prices negotiated by the Centers for Disease Control and Prevention (CDC)—at 35 percent to 80 percent below the prices they charge to the private sector. The federal government, the largest purchaser of childhood vaccines in the United States, negotiates its procurement contracts *de novo* on an annual basis.

Low prices are also given by international manufacturers to international donor agencies for bulk procurements of vaccine for use in developing countries. The low prices provided to UNICEF by core suppliers in Europe, Canada, and Japan are part of a strong tiered pricing system in which developed countries pay a higher price to cover the majority of overhead and R&D costs, plus a moderate return for the manufacturer (Mercer Management Consulting, 1994), thus permitting lower prices to the agency for use in developing countries.

Outcomes

Tiered pricing has made it possible for UNICEF to afford support to lower-income countries for childhood immunization programs, a major contribution to substantial increases in coverage over the past decade. A management analysis commissioned by UNICEF concluded that "the benefits of tiered pricing extend beyond the developing world to the manufacturers and the industrialized countries," since the latter would be forced to pay higher prices if the very large, high-volume UNICEF market did not exist. The volumes involved are seen as sufficient to "move the market" (Mercer Management Consulting, 1994).

Issues

The Mercer analysis concluded, however, that the benefits accruing both to UNICEF and to manufacturers would be greater were the agency to identify and supply vaccines only to the countries most in need. UNICEF procurement currently absorbs 40 percent to 60 percent of the manufacturers' total output of a given vaccine and discounted prices on vaccines are not necessary for countries that can now afford to pay the full price of production. The argument was made that, if UNICEF targeted vaccine procurement services only to countries most in need, manufacturers might, in exchange, be more willing to help achieve other agency goals such as access to new vaccines (Mercer Management Consulting, 1994).

Thus, in November 1994, UNICEF announced a new "vaccine support strategy" that will make procurement decisions targeted toward countries in greatest need. Manufacturers are pleased with this decision, noting that it will contribute to making vaccines more highly valued and therefore move immunization higher on country lists of priorities. The new strategy is also reassuring for companies that have been skeptical about the rewards of discounted vaccine procurement (CVI, 1996).

The United States stopped bidding on the UNICEF market in the 1980s when concerns were raised in the U.S. Congress that the American consumer was subsidizing vaccines for the developing world and thereby elevating the costs of vaccines to the U.S. market. It may be that Congress is now more aware of the benefits of tiered pricing and might be more receptive to policies encouraging such practices. Differential pricing might also have additional appeal in the budget-cutting climate on Capitol Hill as a form of indirect or "off-budget" foreign assistance spending (IOM, 1995).

Nevertheless, concerns remain that expanded U.S. government purchase could be detrimental to the vaccine industry's reliance on profits from sales to private providers. The "Vaccines for Children" initiative enacted by Congress in 1993 was designed to supply vaccines to U.S. children uncovered by health insurance. While the procurement volumes increased correspondingly, the imposition of price caps was viewed most negatively by the vaccine industry. The end result predicted at the time was a diminution in industry cash flow of from $90 million to $120 million a year, with funds available for vaccine R&D dropping as a consequence by $30 million to $40 million. The Mercer analysis noted that this shift already establishes the federal government as the driver of the vaccine business (Mercer Management Consulting, 1996); if the government became the sole purchaser of all pediatric vaccines, the little competition that exists among vaccine manufacturers in the United States would diminish even further (IOM, 1993).

References

Cohen J. AIDS vaccine trials: Bumpy road ahead. *Science* 251:1312-1313, 15 March 1991.

CVI Forum. Special Vaccine Industry Issue 11:13, June 1996.

IOM. *The Children's Vaccine Initiative: Achieving the Vision*. VS Mitchell, NM Philipose, and JP Sanford, eds. VS Mitchell, NM Philipose, and JP Sanford, eds. Washington, D.C.: National Academy Press. 1993.

IOM. The Children's Vaccine Initiative: Continuing Activities. GW Pearson , ed. Washington, D.C.: National Academy Press. 1995.

Mercer Management Consulting. *Summary of UNICEF Study: A Commercial Perspective on Vaccine Supply*. New York: Mercer Management Consulting. 1994.

Mercer Management Consulting. Report on the United States Vaccine Industry, June 1995. New York. In *CVI Forum*, Special Vaccine Industry Issue 11:13, June 1996.

Research and Development Tax Credit

Background

In 1981 under the Economic Recovery Tax Act (PL 97-34) Congress established the R&D tax credit (Sec. 41) to encourage increased research and development activity in the United States and to enable U.S. companies to compete more effectively in the global marketplace. The R&D tax credit lowers the cost of investment in qualified research activities by providing a 20 percent tax credit on incremental R&D spending. The statutory 20 percent rate is applied to the excess of research spending for the current taxable year over a base amount. The base amount for the current year generally is computed by multiplying the taxpayer's "fixed base percentage" by the average amount of the taxpayer's gross receipts for the 4 preceding years. If a taxpayer incurred qualified research expenditures and had gross receipts during each of at least 3 years from 1984 through 1988, then that company's "fixed base percentage" is the ratio that its total qualified research expenditures for the 1984–1988 period bears to its total gross receipts for that period (subject to a maximum ratio of .16). In computing the credit, a taxpayer's base amount may not be less than 50 percent of its current-year qualified research expenditures. As a result of these "caps," as well as because any credit taken must be subtracted from the amount of R&D outlays that can be "expensed" (taken as a deduction in the first year, under Sec. 174), the effective rate of the credit can be reduced to 6.5 percent for firms with high R&D-to-sales ratios (over 32 percent) during 1984–1988, or whose R&D-to-sales ratio has more than doubled since this base period.

Sec. 41 was amended in 1996 to add an "alternative incremental research regime" (AIRC). The electing taxpayer is assigned a three-tiered fixed-base

percentage (for computing qualified research expenses exceeding a base amount computed with respect to average gross receipts for the 4 preceding years) scaled up to 2 percent, with a parallel credit rate scaled up to 2.75 percent. This provision was added to make a research tax credit available to a broader base of companies that would not otherwise be able to claim the 20 percent credit.

Outcomes

The credit has been extended 7 times (with a lapse period from mid-1995 through mid-1996), most recently through May 31, 1997. Under current revenue reconciliation legislation being considered by Congress, the credit would be extended either through December 31, 1998 or December 31, 1999. The effectiveness of this credit in influencing company decisions to pursue high-risk, high-cost, long-term R&D in advanced technology "at the margin" has been adversely affected by congressional action to extend the credit only for short periods.

Issues

A principal factor affecting the long-term extension of the credit continues to be revenue cost, despite independent studies showing economic and revenue benefits from increase in the ratio of R&D spending to output, associated with the credit.

Other current provisions under Sec. 41 provide for a separate 20 percent credit on corporate contributions over a "basic research floor" for basic research conducted by universities; treat 75 percent of amounts paid to a research consortium as eligible for the credit; make 65 percent of "contract research" expenses eligible for the credit, and apply a fixed-base percentage (3 percent, as further recomputed under a 1993 amendment) on qualified expenditures by "start-up" firms.

Puerto Rico/Possessions Tax Credit (Sec. 30a/Sec. 936)

Background

Section 936 of the U.S. tax code was enacted in 1921 to stimulate the economy of Puerto Rico through provision of tax incentives for companies that set up facilities and provided jobs in the Commonwealth. The tax credit was perceived as beneficial to the island's economy, accounting for one-third of total employment, and was also credited with enhancing U.S. competitiveness and establishing Puerto Rico as a viable market for goods produced in the United States.

Outcomes

The Small Business Job Protection Act of 1996 generally repealed the Puerto Rico and possession tax credit. However, U.S. corporations that had active business operations in Puerto Rico or another U.S. possession on October 13, 1995 may continue to claim credits applied to possession business income under Sec. 936 (percentage limitation, or income-based credit) or Sec. 30A (economic activity limitation, or wage-based credit) for a 10-year transition period, subject to limitations on allowable credits under the Omnibus Budget Reconciliation Act of 1993, and a cap (based on the corporation's pre-1996 possession business income) on eligible income as provided in the 1996 legislation. The tax credit for passive income (qualified possessions source investment income) was generally repealed for taxable years beginning after December 31, 1995.

Under the Clinton Administration fiscal year 1998 budget proposal, the Sec. 30A wage-based credit would be extended with respect to operations in Puerto Rico, and the income cap would be eliminated, as would the limitation of eligible corporations to those with preexisting operations in Puerto Rico. The 10-year transition period for the Sec. 936 income-based credit would be maintained. The government of Puerto Rico is pursuing congressional passage of a similar proposal in 1997.

Issues

Limitations on these tax credits enacted by Congress in recent years, with consequent estimated revenue gains, have been based primarily on congressional efforts to reduce the U.S. budget deficit.

CAMPAIGN AND DISEASE-FOCUSED MECHANISMS

Breast Cancer

Background

The Komen Foundation, started in 1982 by Nancy Brinker in memory of her sister who died of breast cancer, has been a critical element in putting breast cancer on the U.S. national agenda. The foundation's first large event included Betty Ford as the guest of honor and later, in 1988, Vice President Quayle and his wife agreed to host Brinker's annual five-kilometer "Race for the Cure" in Washington, D.C. This publicity brought the foundation—and breast cancer—into the spotlight.

The Komen Foundation has raised over $65 million for breast cancer research, education, screening, and treatment, most of it raised within the last 5 years. Other foundations and organizations, created in the 1980s to educate and

support breast cancer screening and research, have raised additional funds. Corporate sponsorship has become fashionable: Ralph Lauren, Revlon, Avon, and Estee Lauder have all established breast cancer foundations or developed dedicated funds—a trend which benefits both corporations and funding for the cause itself. Breast cancer has been deemed a "safe" area for corporate sponsorship and eleemosynary efforts in this area appear to elicit client loyalty.

The strength of these initiatives has been durable, benefiting as they do from huge advertising budgets and their founders' influence on the media (Belkin, 1996), and they continue to be able to generate mass awareness and attract research money, money that has both expedited research, either as start-up funds or as bridge funding that carries researchers through lag times while awaiting approval of larger federal grants.

The formation of the National Breast Cancer Coalition (NBCC), created as a grassroots efforts in 1991 with a mission "to eradicate breast cancer through action and advocacy," has been another powerful tool for the cause. Its "Do the Write Thing" campaign in 1992 generated more than 600,000 letters to Congress, which subsequently doubled the budget allocation for breast cancer research. The Coalition's writing campaigns continued to grow and, in 1993, a campaign to collect 2.6 million letters (representing the number of women living with breast cancer) declared breast cancer a national health emergency (NBCC, 1996).

Outcomes

In 1993, President Clinton called for the design of a National Action Plan on Breast Cancer. In 1994 and 1995, the NBCC successfully fought for continuation of the Department of Defense peer-reviewed breast cancer research funding at a level of $150 million, as well as for greater appropriations for the National Cancer Institute (NCI), as a result up from $265 million in 1994 to $324 million in 1995. Federal financing for breast cancer is currently more than $550 million annually (NBCC, 1996).

Issues

There are concerns in the scientific community that activists, demanding a say on how research dollars are spent, could ultimately do a disservice to basic science. The chief worry is that disease popularity will be the major factor in determining how research money is allocated (Marshall, 1993), a concern that has been raised in connection with HIV/AIDS. There is also concern among breast cancer activists that corporate charity is "fragile" and perhaps, at times, exploitative (Belkin, 1996).

References

Belkin L. How breast cancer became this year's cause. *New York Times Magazine* , Section 6, 22 December 1996.

Marshall E. The politics of breast cancer. *Science* 259:616-617, 29 January 1993.

National Breast Cancer Coalition (NBCC), Home Page. [Online] (http://www.natlbcc.org:80/).

Hiv/Aids

Background

Early awareness of the problem of HIV/AIDS encountered reluctance in the homosexual community to campaign actively on behalf of what was then termed "gay cancer," partly because of fears of evoking increased homophobia. Since 1981, activists have educated themselves in all areas of the knowledge base necessary for confrontation with the powerful government and industry "establishments" that offered the greatest probabilities of finding a cure for the disease.

The ability of this advocacy group to gain access to the channels necessary to change policy and capture the attention of drug manufacturers is largely thought to be a result of its composition—primarily middle-class, well-educated, articulate individuals already organized by a unifying political agenda (Wachter, 1992). The solidity of its organization permitted the AIDS community to focus its message and precipitate change.

The first tactic of AIDS activist groups was to expand access to experimental drugs by questioning the fundamental regulatory core of the drug development process and the system of increased regulation that had been developing since the 1962 thalidomide tragedy. Although that tragedy did not involve U.S.-based companies, after 1962 Congress expanded the role of the FDA, giving it more responsibility for policy decisions and requiring it to evaluate the efficacy as well as the safety of pharmaceutical products. While these regulations were implemented for the safety of the public, the societal price, according to many analysts, was a slowing of medical advances. After some substantial successes in modifying regulatory processes relevant to research and development of AIDS vaccines and therapies, AIDS activists continued to work on obtaining increased appropriations for AIDS research (Rothman and Edgar, 1991).

Outcomes

In response to activists, in 1987 the FDA issued regulations that allow treatment with investigational new drugs (INDs) before full approval of the

drugs for marketing has been granted. In 1988, the FDA also modified its ban on importation of drugs to permit importation of AIDS-related therapies in small quantities for personal use. Activists have also led drug companies to lower prices and are partially responsible for pressuring Congress into allocating $1.7 billion a year for AIDS research (Rothman and Edgar, 1991). "The success of AIDS activists demonstrated that decisions about the allocation of resources—even in health care—are inherently political and thus amenable to effective lobbying" (Wachter, 1992).

Issues

There are fears that relaxation of drug access regulations, now requiring only that a drug show promising test results and no sign of major toxicity, may be excessive. Another concern is that modification of the drug importation ban makes the prospects of clinical trials much more difficult, since the potential combination of drugs makes true evaluation of efficacy impossible (Rothman and Edgar, 1991).

As HIV/AIDS has increasingly affected a more diverse population, priorities have become more various and activists have been concerned that the resulting, less focused approach will be detrimental (Wachter, 1992). There are concerns that, because disease "popularity" drives funding allocations, a more actively promoted disease pulls funding away from less actively promoted diseases (Marshall, 1993)—in other words, a zero-sum game.

Another issue revolves around the perception that treatment for HIV has taken precedence over vaccine development. Because activists have demanded treatment, industry, looking for profits, has responded with the development of drugs that are financially beyond the reach of most of the rest of the world. "From a public health point of view, the rational approach to AIDS would have been to develop a vaccine to prevent it from spreading to the masses rather than creating a chemical that might save a few" (Carr, 1996). The observation has been made that homosexual men in the developed world, who have tremendous influence in the AIDS lobby, may be doing disservice to the rest of the world by lobbying so effectively for "remedies only for the wealthy" and that AIDS may be the first viral disease for which drugs are developed before an effective vaccine, with the possible consequence that "no vaccine is ever developed" (Carr, 1996). These sentiments were echoed at the 11th International Conference on AIDS, where leaders in the global effort against AIDS voiced concerns that costly treatments for those already infected are diverting money and attention away from a vaccine that will prevent new infections (Knox, 1996).

References

Carr G. The profits and the losses of AIDS. *The Economist*, pp. 85–86, 13 July 1996.

Knox R. AIDS vaccine research loses favor; at conference, a call to restart effort. *Boston Globe*, National/Foreign section, p. 2, 8 July 1996.

Marshall E. The politics of breast cancer. *Science* 259:616–617, 1996.

Rothman DJ, and H Edgar. AIDS, activism, and ethics. *Hospital Practice* 26(7):135–142, 1991.

Wachter R. AIDS, activism, and the politics of health. *New England Journal of Medicine* 326(2): 128–133, 1992.

Juvenile Diabetes Foundation

Background

The Juvenile Diabetes Foundation (JDF), founded in 1970 by the parents of children with diabetes, is a not-for-profit, voluntary health organization with U.S. chapters and international affiliated chapters worldwide (Australia, Brazil, Canada, Chile, France, Greece, India, Israel, Italy, Puerto Rico, and the United Kingdom). Parents' realization that the discovery of insulin was not a cure for diabetes prompted them to create a resource that would educate the world about the serious, life-threatening complications of this disease and promote the collaborations necessary to discover a cure.

To accomplish this goal, JDF has focused on funding scientific research. The establishment of Diabetes Interdisciplinary Research Programs (DIRPs) beginning in 1992 has been one such commitment. Also referred to as "Programs of Excellence," these interdisciplinary research programs were created to bring together scientists from a variety of fields to work in collaboration with diabetes investigators and to combine their expertise. Over the last 27 years, the JDF has become the world's leading voluntary health agency funding diabetes research, awarding $31.3 million worldwide in 1996, bringing its cumulative commitment to research since 1970 to $211 million.

JDF attributes much of its success to its grassroots volunteers. While the organization's public/private partnerships have been successful, the bulk of its funding has been raised by volunteers at the chapter and affiliate level. Volunteers have also been influential in persuading Congress to increase fiscal year 1997 funding to NIH, particularly to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Special events, including golf tournaments, fashion shows, and a new planned giving program to generate income through bequests, trusts, life insurance policies, and real estate gifts, have all helped the JDF achieve its goals. Its "Only Remedy Is a Cure" campaign, launched in 1990, pioneered the concept of public/private funding partnerships, bringing together money from government to match private gifts

from individuals, foundations, and corporations. The campaign exceeded its original goal of raising $100 million and now seeks to raise $200 million by the year 2000.

Outcomes

The JDF now collaborates with four of the National Institutes of Health, the U.S. Department of Veterans Affairs, and the Medical Research Councils of Canada and Australia. It has created programs that bring together leading diabetes researchers with scientists from many institutions and disciplines. With the addition of 12 new $5 million DIRPs in 1996 (double the number in 1995), there are now DIRPs operating in 26 academic health centers throughout the world. Over the last 25 years, the JDF has been influential in persuading the U.S. government to increase diabetes-related research allocations from $18 million to $300 million.

Issues

The Juvenile Diabetes Foundation believes that the federal government must increase its commitment to biomedical research funding and that reducing funding to NIH would be detrimental to the basic research necessary for a cure for the disease (JDF, 1996).

References

Clark W. Epic Research. 1997 *Research Progress Report Countdown* XVII (1), Winter 1997.
Juvenile Diabetes Foundation (JDF). *Annual Report 1995*. New York, 1996.
Juvenile Diabetes Foundation International (JDFI). *Department of Finance and Administration Fact Sheet*. 1996.
JDFI. *JDF's Diabetes Interdisciplinary Research Programs Fact Sheet* . 1996.
JDFI. Government Relations. *Diabetes Demands a Cure*. 1996.

ORGANIZATIONAL MECHANISMS

International Vaccine Institute

Background

The International Vaccine Institute (IVI) was initiated by the United Nations Development Program (UNDP) within the framework of the Children's Vaccine

Initiative (CVI), a coalition of international and national agencies, national governments, nongovernmental organizations, and publicand private-sector vaccine companies.

In 1992, a UNDP-sponsored feasibility study examined the availability of resources and policy commitment to sustain a new institute devoted to vaccine research and development and to promotion of technical cooperation. A site selection process followed, focusing on the Asia-Pacific region because of its expanding economic resources, rapid industrial growth, and progress in vaccine science. In 1994, Seoul, South Korea, was selected to house the IVI, at present the only international research center dedicated to vaccine research and development for the developing world. The institute will not produce vaccines but will work cooperatively with international organizations, national institutions, nongovernmental organizations, industry, and health and vaccine specialists to catalyze, facilitate, and stimulate new vaccine research and introduction by other concerned organizations (IVI Home Page, 1997). A major role of the institute will be to forge strong cooperative partnerships with the commercial sector to lower the high entry barrier that now exists for new vaccines and new vaccine formulations designed for public sector use (IVI Home Page, 1996/7).

Outcomes

Representatives of 12 member states of the United Nations and a representative for the World Health Organization (WHO) met on October 28, 1996, to sign the agreement to establish the IVI. The Establishment Agreement came into force on May 29, 1997. The institute has made substantial progress in establishing links with key centers around the world and appears to be building a solid basis for cooperation and collaboration with industry (IVI *Newsletter*, 1996). In January 1995, initial operation of the institute began with a core staff at interim offices at Seoul National University. The headquarters building is currently scheduled for completion around the end of 1999. The institute estimates a full-time staff of 200 with about 70 percent engaged in scientific research (IVI Home Page, 1996).

Issues

The IVI believes that collaboration with private industry is essential for putting new and improved vaccines into use in developing countries. It has identified Haemophilus influenzae B (Hib) vaccine as a first target area. In Asia there is some uncertainty about the extent and disease burden of Hib infection and there is low interest in Asian countries for Hib vaccines that have had such a dramatic impact in developed countries. The IVI is launching a multi-site, multi-country study to assess the disease burden of Hib infection. The project is being

developed in close collaboration with the major manufacturers of Hib vaccines, including Merck and Lederle in the United States. The manufacturers will serve on a project management committee and have indicated their intention to provide technical and financial support. The goal of the project, if a significant disease burden is found, is to lay the groundwork for the introduction of Hib vaccines. The IVI believes that this project has the potential to provide significant benefit to Asian countries and to facilitate the efforts of industry to broaden their vaccine distribution.

Of substantial importance to U.S. companies is respect for intellectual property rights, and there has been great interest in seeing what policies the IVI would adopt with respect to this matter. The IVI board of trustees has enunciated a policy of full respect for intellectual property rights. This policy includes provisions for the fair and equitable licensing of intellectual property rights that may come into the possession of the institute. Finally, the IVI has committed itself to a full review of intellectual property rights issues and to conducting the review in consultation with relevant U.S. government agencies such as the Departments of State and Commerce.

References

International Vaccine Institute (IVI). *Newsletter* 3, November 1996.
IVI. Home Page. [Online] (http://www.dacom.co.kr/~vaccines) 1996-1997.
IVI. Under the Umbrella of the CVI. Brochure. 1996.

International AIDS Vaccine Initiative (IAVI)

Background

The International AIDS Vaccine Initiative (IAVI) was established in 1996, with the mission of ensuring development of safe, effective HIV vaccines for worldwide use. The initiative is to accomplish its goals through three areas of activity: 1) advocacy for HIV/AIDS vaccine research and development; 2) support for a highly targeted applied vaccine development effort focused on gaps in current research and development; and 3) work with government, private industry, funders, and regulatory authorities to create a more favorable environment for increased investment. The IAVI will work collaboratively with developing country researchers, national programs, and international agencies to develop and test existing and future vaccines in developing countries, along with continued research and testing in industrialized countries.

The IAVI also intends to increase existing scientific efforts in areas of applied research to determine the effectiveness of HIV/AIDS vaccines. It will not, itself, do research but, rather, will fund yearly those two to four key research and development projects that will best benefit HIV vaccine

development. The IAVI will spend approximately $2 to $4 million in 1997 to accomplish its goals; the first grantees were identified in 1997 (Secretariat, 1996). In addition, the IAVI is searching for an experienced vaccinologist as a CEO. Once a person is on board, a series of activities will be developed in consultation with industry to improve the environment for commercial HIV vaccine development. This may include work on liability, creating a commercially viable market in the developing world, distribution issues for noncommercially viable markets, and other areas.

Outcomes

An active advocacy campaign has focused more attention on vaccines domestically and internationally. In addition, the IAVI has recently announced its first year's scientific plan which will include the funding of two primary scientific areas of emphasis: 1) development of HIV-DNA vaccines and 2) expanded safety studies of live-attenuated HIV. The organization is seeking partners to collaborate in preclinical trials with HIV-DNA vaccines and to address safety concerns and possible risks and benefits of pursuing human trials using a live-attenuated HIV vaccine. The IAVI is supported by the Rockefeller, Sloan and Until There's a Cure foundations, UNAIDS, the World Bank, and a variety of other donors.

Issues

The exploration that led to IAVI was started in 1993, at a time when vaccine research was at a nadir. Vaccines were the lowest funding priority in the public sector and little work was going on in the private sector. Over the last few years, there has been an increase in interest in vaccines, including more activity in the public and private sectors. In the United States, however, the bulk of public funding has been allocated toward the basic sciences. IAVI applauds this work and the IAVI intends to complement this funding by addressing what it perceives as a funding deficit in the area of applied science.

The organization is also concerned about the fact that almost all experimental HIV vaccines have been based on the single genetic subtype most prevalent in the United States and Europe. While the significance of genetic subtypes in vaccines remains unknown, it seems pragmatic to test vaccines based on subtypes more prevalent in the developing world, which have not received adequate attention. A further concern has to do with the increasing complexity of intellectual property rights (IPR). For example, production of the new, genetically engineered hepatitis B vaccine requires 14 patents, generating costs that are reflected in the vaccine's pricing. In an effort to develop vaccines that will be accessible to everyone, the IAVI convened a meeting in August 1996 to discuss IPR issues. The recommendation from the meeting was that the

IAVI should work to protect the intellectual property rights of research it funds, thus facilitating access to other patents and providing incentives for industry to work with the IAVI in development and distribution of an HIV vaccine. The goal would be to make vaccines available to those living in extreme poverty where adequate commercial markets just do not naturally exist. The pivotal question is how to accomplish that (Nelson/IAVI, 1997). Industry's reluctance to invest in HIV vaccines is derived from pessimism about whether vaccines would work, as well as a from general "lack of good ideas"; however, with the advent of DNA vaccines, companies are now more likely to get involved (Plotkin/IAVI, 1996).

References

Bhamarapravati N. Studying AIDS vaccines in Thailand: An Interview with Nath Bhamarapravati. *IAVI Report* 2(1): 4–5, Winter 1997.

Nelson L. IAVI Issues—Report on Intellectual Property Rights. *IAVI Report* 2(1):7, Winter 1997.

Plotkin S. Industry Perspective: An Interview with Dr. Stanley Plotkin. *IAVI Report* 1(1):6–7, 12, Summer 1996.

Secretariat (*ad interim*). *International Vaccine Initiative—Scientific Areas of Emphasis*. 1996.

Inter-Company Collaboration for Aids Drug Development

Background

In April 1993, 15 pharmaceutical companies agreed to collaborate to facilitate—through the sharing of information and drug supplies—the conduct of early combination and comparative studies of antiviral agents for the treatment of HIV infection and AIDS. Those companies formed the "Inter-Company Collaboration for AIDS Drug Development," with the purpose of better enabling each of them to independently evaluate new antiviral investigational drugs for potential clinical benefit, either alone or in combination with marketed or investigational drugs of other companies. By sharing relevant preclinical and clinical data (including negative data on antiviral compounds that have failed in drug development), facilitating access to investigational drug supplies, and developing standardized preclinical assays and procedures and other activities, the companies hope to accelerate the development of promising new drugs and identify combinations of antiviral drugs that will significantly advance the treatment of HIV infection.

Outcomes

Eighteen companies now participate in the Collaboration: Agouron, AB Astra, Aji Pharma USA, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Ciba-Geigy, DuPont Merck, Gilead Sciences, Glaxo Wellcome, Hoechst AG, Hoffmann-La Roche, Merck, Pfizer, Pharmacia & Upjohn, Sigma-Tau, SmithKline Beecham, and Triangle Pharmaceuticals.

The Board of Participants, comprised of R&D heads of the member companies, was established in July 1993 and is the general oversight body responsible for the implementation of the Principles Governing the Collaboration. Operating expenses are shared equally among member companies. The Board of Participants met several times in 1993, 1994, 1995, and 1996.

Several standing committees reporting to the Board were appointed, including the Scientific Panel, Legal Committee, Communications Committee, Nominations Committee (to review new membership applications), and liaison committees (to facilitate various sorts of exchange among the concerned communities).

The objectives of the Scientific Panel are to facilitate: 1) exchange of scientific information; 2) sharing of animal model technology for antiviral research; 3) provision of compounds and the conduct of combination trials; and 4) virological assay validation and method standardization.

The Scientific Panel met with the Board of Participants several times in 1993, 1994, 1995 and 1996. In the course of those meetings, scientific disclosures on different antiviral programs were made by Hoffmann-La Roche (saquinavir; TAT antagonist), Bristol-Myers Squibb (d4T), Merck (protease inhibitor indinavir and non-nucleoside reverse transcriptase inhibitor L-697,661), Glaxo Wellcome (3TC™; protease inhibitor VX-478; nucleoside reverse transcriptase inhibitors 935U83 and 1592U89), Astra Foscavir®), Boehringer-Ingelheim (nevirapine), Hoechst (pentoxifylline), Eli Lilly (former Collaboration member) (non-nucleoside reverse transcriptase inhibitor LY 60046), Aji Pharma USA (lentinan, curdlan sulfate), and Hoechst and Bayer (non-nucleoside reverse transcriptase inhibitor HBY097).

The Scientific Panel also appointed a Virology Subcommittee, to standardize and validate assay procedures and methodologies, develop a database of HIV antiviral drug resistance, and facilitate exchange of biological data and viral constructs among member companies for resistance/cross-resistance testing. The Virology Subcommittee quickly established a standard protocol for measurement of *in vitro* antiviral activity, using consensus cell system, virus strain, and a number of standard reagents. The Subcommittee is developing standardized cytotoxicity and primary isolate susceptibility protocols, as well as a database of HIV antiviral resistance.

The Scientific Panel also appointed a Clinical Trial Subcommittee with the primary objective of developing a consensus protocol for clinical evaluation of multi-drug combinations of antiviral agents, both investigational and marketed.

The committee produced a master protocol, identified the first three-drug combinations for clinical evaluation, and recommended two contract research organizations, one to implement and monitor the evaluation, the other to implement and monitor the initial studies. Enrollment for the first study, ICC Protocol 001, which evaluates combinations of AZT/ddC/nevirapine and AZT/ddC/saquinavir with AZT/ddC as the control arm, was completed in June 1995. The second study, ICC Protocol 002, started in September 1995 and will evaluate combinations of AZT/ddI/nevirapine and AZT/ddI/3TC, with AZT/ddI as the control arm. Additional studies of triple-combination antiviral drug regimens are under development.

Regional System for Vaccines/Sistema Regional Para Vacunas

Background

The Regional System for Vaccines/Sistema Regional para Vacunas (SIREVA) was developed within the framework of the Pan American Health Organization (PAHO) in 1993. SIREVA is an international programming, administrative, and coordinating initiative to improve the quality, effectiveness, and cost of vaccines by working to coordinate all stages and participants involved in vaccine development and production for the people of Latin America and the Caribbean. The need for such a focus emerged from the realization that the costs of many newly developed vaccines were going to be prohibitive for the countries of this region. Technical cooperation among those countries will make it possible for them to produce the new vaccines needed (PAHO/World Health Organization [WHO], 1994). Cooperative efforts are under way with PAHO's Special Program for Vaccines and Immunization (SVI) to accelerate research, development, production, and quality control measures of vaccines. SIREVA proposes to take advantage of a number of centers throughout Latin America and, through coordinated action, develop the necessary knowledge, scientific, and technological capacity and means to develop, produce, and maintain quality control of immunizing agents to combat diseases relevant to Latin America and the Caribbean (Wittenberg, 1994).

Outcomes

Over the years, SIREVA has received support from the Government of Mexico, the Rockefeller Foundation, the Inter-American Development Bank, the World Bank, the United Nations Children's Fund (UNICEF), the United Nations Development Program (UNDP), and the International Development Research Center (IDRC/Canada). SIREVA is working on a regional network of quality control laboratories to start quality control training programs, and is working as well on a program for providing centralized certification

mechanisms for diptheria-tetanus-pertussis (DTP) producers in the region. The promotion of research on vaccines of regional interest also heads the SIREVA agenda (CVI, 1996) and the organization has developed a master plan for each currently investigated vaccine that will serve to coordinate implementation of several phases of vaccine development (EPI, 1995).

References

CVI Forum. *Special Vaccine Industry Issue* (11). Geneva: World Health Organization, 1996.

EPI Newsletter. Ensuring the Production of Vaccines in the Region. XVII:6, December 1995.

Pan American Health Organization (PAHO). *Regional System for Vaccines for Latin America and the Caribbean (SIREVA)*. Washington, D.C.: PAHO/WHO. 1994.

Wittenberg R. Testimony of Richard L. Wittenberg, President and Chief Executive, American Association for World Health, Before the Subcommittee on Foreign Operations Export Financing and Related Programs, Committee on Appropriations, U.S. House of Representatives, Washington, D.C.: Federal Document Clearing House. 1994.