C V I F O R U M

SPECIAL VACCINE INDUSTRY ISSUE

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In this issue

CHILDREN'S VACCINE INITIATIVE

New leaves

The Children's Vaccine Initiative (CVI) is a coalition of international and national agencies, national governments, non-governmental organizations, and public- and private-sector vaccine companies. It was established in 1991 to promote, coordinate and accelerate the development and introduction of improved and new vaccines and thereby enhance the protection of the world's children against infectious diseases.

Exceptionally, this 11th issue of *CVI FORUM* has only a single article on a single topic: the vaccine industry. I believe the importance of the topic justifies our breaking with the editorial tradition set by the first 10 issues.

Industry is a key partner – an essential partner, in fact – in the CVI's efforts to accelerate the development and deployment of new and better vaccines for the world's children. The CVI-industry partnership may well be a model for the more general relationship between the public and the private sectors. Understanding the setting within which that relationship has evolved is to have a clearer notion of the forces – the biases, the one-sided motivations, the misconceptions – that have kept it from achieving its full potential. And, conversely, of the factors that in the last two or three years have brought about what many observers see as a breakthrough in the relationship.

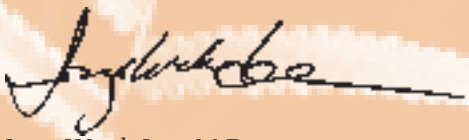
This issue of *CVI FORUM* attempts to show, through the opinions and perspectives of some of the key players, how far we have come in forging a true partnership. It also describes some of the obstacles still cluttering the road ahead. We have, I believe, come a long way. And we will, I am sure, take the obstacles in our stride.

On this Spring day, as I write these lines, the trees are bristling with fresh green leaves. The air is full of a renewed energy. Everything points to the warmth and fulfilment of the coming summer.

That's how I feel about the vaccine industry. It is bustling with new energy – from the amazing new powers of science, from the new biotechnology industry that has sprung up to take advantage of these powers, from the new markets that are opening up in the developing world. There have never been so many new vaccines or vaccine combinations under development. Everything seems to be on the move.

This is surely a good time for us, the public and private sectors, to take stock together and to look to the fulfilment of the summer ahead.

The following pages will, I hope, if nothing else, help you to understand and share my optimism.



Jong-Wook Lee, M.D.
Executive Secretary
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Cover photo: Science Photo Library/G. Tompkinson

Public sector, private sector: discord or dialogue?

Facing off across the rift

Not so long ago the vaccine world was as easy to understand as the political world during the Cold War. There were essentially only two sides to worry about. On the one, the private sector – motivated, at least in industrialized countries, mainly by profit, but efficient, dynamic, productive. On the other, the public sector – devoted mainly to bettering public health, but often mired in institutional inertia and, on the international stage, hostage to the wiles and whims of individual countries. And in between, at worst a no-man's-land of incomprehension, at best a shaky bridge of shared humanitarian motives on which the two sides would occasionally reach out to each other as far as their ideologies would allow.

Exaggerated?

Not according to a recent U.S. report[1], which noted that, "historically, the relationship between industry and government has been ... adversarial and parochial."

Nor according to Dr Bill Hausdorff, who is struck by "the enormous amount of antagonism there has been between public and private sectors on vaccines." He should know. He recently leaped across the divide from manager of a children's vaccine project at the United States Agency for International Development (USAID) to become associate director for scientific affairs with one of the three largest US-based vaccine suppliers, Wyeth-Lederle Vaccines & Pediatrics of West Henrietta, NY. "A lot of people at WHO and other development organizations really thought that the for-profit producers are not particularly interested in people's health. And a lot of people in industry felt that public sector people lack a complete sense of the value of vaccines and of the tremendous effort and expense that go into their development and manufacture. And these stereotypes have precluded effective dialogue."

A similar viewpoint is that of Dr John R. La Montagne, director of the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases (NIAID) in the United States. "One of the sad problems is that implementers and researchers and manufacturers hardly ever got together, and when they did they didn't talk the same language," he remarked recently to a *SCIENTIFIC AMERICAN* reporter.

And at Merck & Company, Inc., one of the largest U.S. vaccine suppliers, Dr Tom Vernon, executive director in the Vaccine Division, described the situation to *CVI FORUM* as "the classic dilemma, where we have the vitality of an industry dependent upon investors, an R & D vitality that cannot easily be achieved in the public sector, but that many people would like to see used for charitable purposes." Dr Vernon, too, is a recent public sector "emigrant," after a long career as Colorado state epidemiologist and health commissioner. "I've been in government all my life and love government service, but deep down I don't believe it can provide the capability, drive and initiative for vaccine development that I see here in industry." The dilemma, Dr Vernon said, "will face us for a long time to come."

The rift narrows

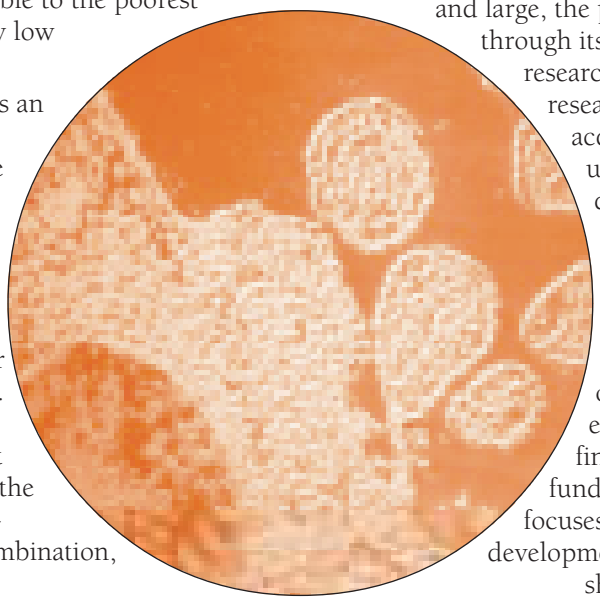
Yet, for some pundits of the vaccine industry, the Cold War analogy *is* an exaggeration. Certainly there have been difficulties and tensions that have tended to keep the public and private sectors on

"Implementers and researchers and manufacturers hardly ever got together, and when they did they didn't talk the same language."

different sides of the fence, but the fence has never been a high one, says Mr Bill Packer. Now president of a U.S. startup biotech company, Virus Research Institute, in Cambridge, Massachusetts, throughout the 1980s Mr Packer headed SmithKline Beecham's global vaccine business. "How," he asks, "would UNICEF and the WHO now be protecting some 80% of the world's children against six potentially lethal or crippling infectious diseases – diphtheria, pertussis, tetanus, tuberculosis, measles and polio – had industry not cooperated in providing high-quality vaccine at low cost for the 130 million children entering the world every year? I don't think enough recognition has been given to the incredible job done by the for-profit vaccine industry in ensuring that supplies of children's vaccine were available to the poorest in the world at very low prices?"

"Industry has been giving the world a tremendous bargain over the years."

Mr Packer cites as an example the polio vaccine that private industry sold at up to and sometimes even over US$10 a dose in developed countries and has sold to UNICEF for 10 US cents a dose. The same tiered pricing was also set for other vaccines, the diphtheria-tetanus-pertussis (DTP) combination, Bacillus Calmette-Guérin (BCG), measles and tetanus vaccines and even for some of the newer vaccines, such as the hepatitis B vaccine that is being sold to developing countries at 5-10% of its developed country price. "You don't make much profit on a 10-cent vaccine. So industry has been giving the world a tremendous bargain over the years. You can call it industry's contribution to development."



A major vaccine target *– measles virus (seen by transmission electron microscopy [TEM] budding from cell surface, magnif. 42,000).* Photo: CNRI

Two stages, two roles, one goal

It may not, for sure, be always uppermost in their minds, but another example of cooperation between the players of the public and private sectors is the acceptance of responsibility by each for a separate stage in the overall vaccine development process. As a report[2] by a U.S. Institute of Medicine committee on the CVI notes: "Basic research is conducted primarily by ... academic and government scientists. Once a basic scientific finding is thought to have ...practical applications, the research moves on to applied R&D...much [of which] and almost all product-development activity are conducted by private industry."

CVI coordinator Dr Roy Widdus views the respective roles of the partners this way: "By and large, the public sector, through its biomedical research agencies, funds research aimed at acquiring a deeper understanding of diseases and their pathogenetic mechanisms. Private industry, which does not fund basic research on diseases to any extent, takes the findings from publicly funded research and focuses it on product development. There is no sharp hand-off point, but the role of public agencies is essentially to do enough to convince industry that a product is feasible. Just what is 'enough' will vary from target to target."

Financially, the private vaccine industry's contribution to R&D on new vaccines amounts to about US$500 million a year, according to Jacques-François Martin, chairman of the Biologicals Committee of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA). Not by any means a piddling sum, but only

Pasteur Mérieux/Service audiovisuel

An R & D target *– administering vaccines to children at risk (here with an experimental jet gun)*

3% of the US$16.6 billion total pharmaceutical R&D expenditure worldwide (which, itself, represents 15-20% of total sales).

To transfer or not to transfer or what to transfer

Industry has also contributed, tentatively, to what in the 1960s and 1970s was one of the public sector's pet objectives, namely the bolstering of local vaccine production capability in developing countries, largely through transfer of technology to developing country producers. But the results have not on the whole been convincing.

One major obstacle to technology transfer has been the lack of effective management systems in many Third World vaccine production facilities, according to Ms Amie Batson, technical officer with the Vaccine Supply and Quality Unit (VSQ) of the WHO's Global Programme for Vaccines and Immunization (GPV). "This black hole of management," she says, "has been partly due to the often restrictive government rules and regulations that many Third World vaccine producers have had to cope with but that were designed specifically for public administrative institutions, not for the type of management that a vaccine production facility requires. And partly, the problem has also been a general absence of a good management culture." The result, locally, is a "difficulty in producing quality vaccines through Good Manufacturing Practice compounded by a difficulty in ensuring the maintenance of sometimes complex modern vaccine technology." More importantly, "lack of good management keeps developing country producers from attaining the levels of economic viability that would put them in a stronger negotiating position for joint venture partnerships with developed country manufacturers."

Such partnerships are viewed by these manufacturers as a condition for transfer of technology and a hedge against their fear that developing country producers, equipped with the know-how and sufficiently large production facilities, might be tempted to infringe patent law and start exporting their vaccine at cut-throat prices.

Another way around the patent problem is a collaborative arrangement whereby developed country producers hang onto the know-how but ship vaccine in bulk to developing country producers for filling and finishing.

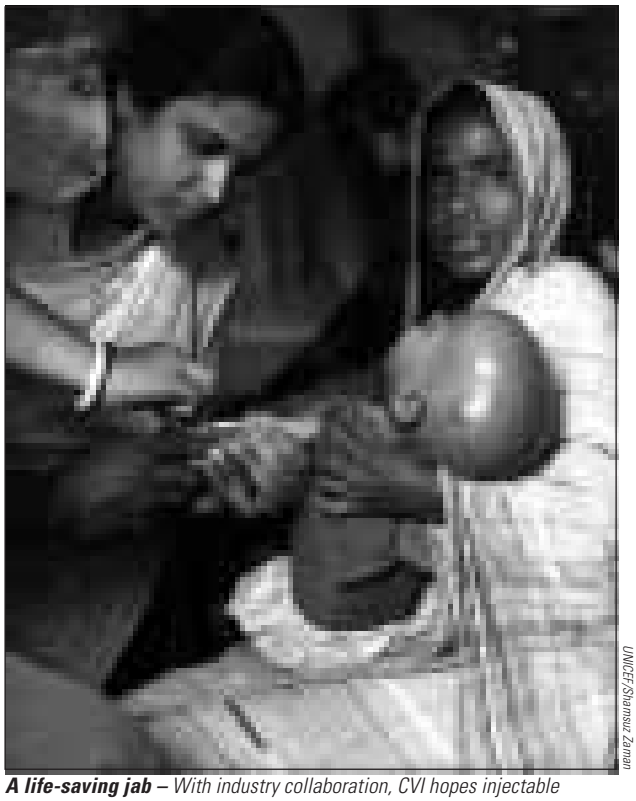
Yet another possible solution is a step-by-step technology transfer process, starting with transfer of bulk vaccine and moving through the more patent-sensitive vaccine development milestones as and when confidence and financial returns warrant it. But, as Ms Batson points out, for such arrangements to work "there has to be a direct relationship between the manufacturer who holds the patent and produces the bulk and the local developing country facility that does the blending and filling."

"This black hole of management has been partly due to the often restrictive government rules and regulations that many Third World vaccine producers have had to cope with."

"We have seen what the realities of technology transfer are and we no longer regard it as a panacea or an end in itself."

Private manufacturers also realize they have to be more selective in their choice of developing country partners. Mr Walter S. Vandersmissen, director for government affairs at SmithKline Biologicals, at Rixensart, in Belgium, doesn't discard the principle of technology transfer but sees a need for "an audit of Third World producers that would show which facilities have economic viability and where their strengths lie." Currently, Dr Vandersmissen believes, the most "attractive" candidate partners are in countries, like Brazil, China, India, Indonesia, Mexico, South Africa and Thailand, that "have large industrial and technical capability."

These are among several countries that have growing middle-class populations offering a sizable private market potential in relatively "untapped" geographic areas of the world.



UNICEF/Shamsuz Zaman

A life-saving jab *– With industry collaboration, CVI hopes injectable vaccines will eventually be replaced by more easily administered non-injectable (oral, ærosol, etc.) vaccines.*

In the end, though, Mr Vandersmissen questions whether technology transfer is really worth the effort: "There is no shortage of vaccine today. So what's the sense in equipping another dozen local producers and cranking up more vaccine that could drive prices down and lead to disruptive practices like dumping by developing country producers in order to keep their plants running."

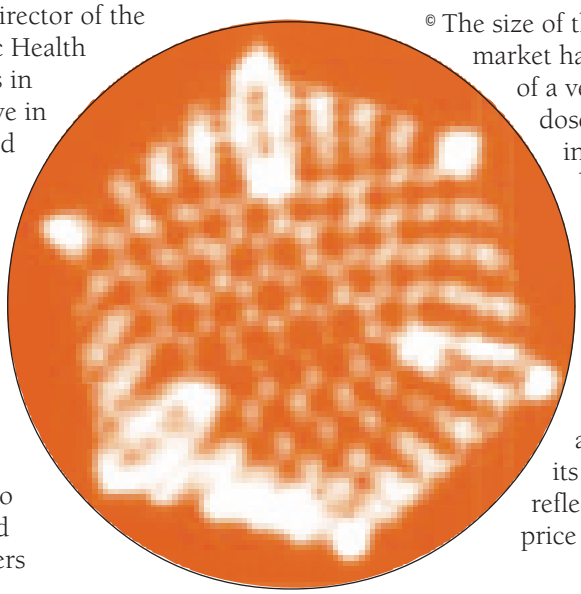
Mr Packer agrees: "It's thanks to developed country technology and its optimization over the past 40 years that huge volumes of high-quality vaccine can today be efficiently produced at the lowest costs. If you transfer this technology and start putting it in smaller pots and pans around the world, you're going to lose the benefits of scale of production you have had with the centralized facilities." What's more, he adds, "it was never as simple as you thought it would be. And Murphy's law was ever-present – what *could* go wrong, *would* go wrong. And whatever figure you had thought it would cost to set up a technology transfer deal, you ended up by having to double it."

The public sector, too, has been revising its strategies for support to developing country producers. "We have seen what the realities of technology transfer are," says Ms Batson, "and we no longer regard it as a panacea or an end in itself." Again, this means being more selective than in the past – selective about which producers in which countries should receive support and what kind of support. "In some cases, filling from bulk might be the best short-term arrangement – as, for example, with vaccines that are highly protected by intellectual property rights and that have a strong industrial country market. But vaccines that don't have such a market but are of a more regional pertinence, like the yellow fever vaccine, might be better produced locally."

For the CVI, helping developing countries to produce, not more vaccine, but better quality vaccine, is now a top priority. Over the CVI's first five years, it has funded work towards this goal, initially through a CVI task force and more recently through the VSQ.

The VSQ team is also helping countries to build up their management systems. Ms Batson says, "We are suggesting to countries ways in which they can become attractive partners to companies in industrial countries willing to provide access to new technologies in exchange for a commercial foothold in the Third World."

Dr George Siber, director of the Massachusetts Public Health Biologic Laboratories in Boston, USA, says "we in the public sector need to develop a mechanism to collaborate with each other, so that we can share technology and help each other with quality control, quality assurance and training, so that we improve our ability to produce vaccines and become better partners for private industry to collaborate with." To this end, Dr Siber has proposed a public consortium of vaccine producers – an idea that the CVI is backing, but more in the form of a vaccine producers' network linking sectors – public and private – and worlds – developing and developed.



A combo target *– the hepatitis A virus (seen here by TEM, magnif. 350,000) and hepatitis B virus will be under attack from several new combination vaccines (page 22).*
Photo: CNRI/A. Pasieka

The pillars of a partnership

When all's said and done, though, selling vaccines to developing countries through UNICEF has been the cornerstone of industry's collaboration with the public sector. The arrangement changed little, year in, year out, over the past decade-and-a-half. It had become so much part of the vaccine landscape that, to the chagrin of many an industry executive, it was being largely taken for granted.

It was made possible, however, by three factors:

© The traditional pædiatric vaccines are relatively simple and inexpensive to make. Moreover, they do not involve processes or components carrying costly intellectual property rights (IPRs) or royalties that would add to the cost per dose of a vaccine. For this reason, the bulk of vaccine production costs – 85% according to the Mercer study – is largely fixed, so that the unit cost falls as the number of doses rises.

© The size of the developing world market has ensured the sale of a very large number of doses – today amounting to about 3.5 billion a year or two-thirds of the world's total vaccine production, according to the Mercer study. (The fact that it contributes to only about a twentieth of its vaccine revenue, reflects the relatively low price industry charges for the traditional vaccines it sells to developing countries.)

© A system of tiered pricing has enabled European vaccine producers to utilize their production capacity to the full and gain access to Third World markets by selling huge volumes of vaccine for developing country markets at prices these countries can afford. At the top tier, producers sell to industrialized country markets at prices that cover basic production and R & D costs plus profit margins. At the lowest tier, they sell to UNICEF at very low prices that cover, not the R & D costs, but only the marginal costs, and contribute to overheads. And at a middle tier, they sell

A system of tiered pricing has enabled European vaccine producers to utilize their production capacity to the full and gain access to Third Word markets.

directly to some developing countries at prices somewhere between levels set for the "home" market and UNICEF prices. U.S. firms have not tapped at all into UNICEF markets, ostensibly because of a domestic social and political climate hostile to the multi-tiered pricing system (see page 10).

UNICEF/ S. Sprague

Team work *– to get vaccines to where they are needed, researchers and industry run the first laps, then pass the baton to health workers for the last dash.*

An uneasy alliance

These were the pillars on which industry collaboration with the public sector traditionally rested and which allowed the public-private sector alliance to endure for almost two decades.

An uneasy alliance, though.

Every so often an industry executive would complain about the public sector's so-called "10-cent mentality," its drive to provide cheap vaccines to as many developing countries as possible – and also to some "semi-developed" countries – regardless of the ability of these countries to pay higher prices, and generally about public sector reluctance to appreciate the true worth of vaccines.

At the IFPMA Mr Martin sums up the industry viewpoint this way: "There is no reason why a vaccine, which protects for life against a deadly disease, resolves the growing problem of resistance to antibiotics, offers the unquestionably best cost-benefit ratio and is probably the only real protection against viral diseases, why such an extraordinary medical contribution should be less costly than a therapeutic drug."

And every now and again a public health official would complain about industry not being responsive enough to the needs of, and opportunities in, the Third World.

"There is no reason why a vaccine, which protects for life against a deadly disease, should be less costly than a therapeutic drug."

When William Hausdorff worked for USAID, he shared this view. "I felt that many companies had a visceral reaction to doing business in the Third World," he recalls. "Part of the problem, I'm sure, was inertia, stemming from cultural differences and part from unfamiliarity with the territory."

Changing the rules of the game

But more importantly, while the bickering continued off-stage, developments were afoot that were soon to throw the entire vaccine community – both private and public – into a turmoil and force both sides to rethink the terms of their alliance.

These were the developments and they took place more or less concurrently over the past two decades:

© Vaccination started to move to the front of the public health stage. Global coverage of children with the basic EPI vaccines was approaching 80% and was believed to be preventing nearly 3 million deaths. Vaccination was driving polio out of the Americas and a major initiative to eradicate the

disease was being mounted. All in all, immunization was getting a good press and creating a demand, at least in public health circles, for more vaccines, better vaccines, new vaccines.

© At the same time, advances in the biomedical sciences – particularly recombinant DNA technology, immunology, biochemistry and microbiology – were fuelling hopes that scientists could meet that demand. That the R&D artisans could improve existing vaccines so as to make vaccination easier, particularly in the developing world. And that they could design new vaccines against still-rampant diseases, like malaria and other parasitic diseases, acute respiratory infections, diarrhoeal diseases, AIDS and other sexually transmitted diseases, and meningitis, for which vaccines don't exist or are not satisfactory and which together are causing about 9 million deaths a year.

© Progress in science and technology was also spawning a new biotechnology industry, with companies staking claim each to its own strip of the new scientific frontier. This time the rush was for vaccine "gold" – new vaccine components (genes, antigens, adjuvants, etc.), vaccine delivery systems (viruses, bacteria, microspheres, etc.), immunizing schedules and procedures, combination processes and formulations, and so on.

© Vaccine development costs were being driven upwards by rising liability insurance and increasingly stringent and therefore costly regulatory requirements. Vaccine prices were also set to rise even further as newer vaccines entered the assembly line requiring new, more costly technology plus an army of lawyers and funding to access essential components bristling with the royalties that the new biotech firms were attaching to them. A new generation of proprietary vaccines, in a different cost – and price – bracket from the traditional EPI vaccines, had already hit the market, providing protection against hepatitis B (Hep B), varicella, *Hæmophilus influenzæ* type b (Hib), and hepatitis A (Hep A). And a host of other vaccines were waiting in the wings.

© Caught between rising costs and fixed or falling prices the vaccine industry underwent a process of rationalization. Many companies abandoned the field: of the 20 internationally active companies producing vaccines in 1960, less than a dozen were left by the early 1990s. Some survived by merging, thereby spreading vaccine development costs over a broad product portfolio and raising production capability to meet the rising demand for vaccines from a large international market – particularly from developing countries whose demand had risen 10-fold in the previous decade and now accounted for over two-thirds of worldwide demand for vaccine doses. Other companies formed links – through joint venture partnerships, licensing agreements and so on – with each other or with some of the new biotech firms, thereby enabling them to access the new vaccine technology, new vaccine components and new geographic markets. Today the vaccine industry is dominated by about

PHOTOTAKE – CNRI

Using life to save life *– chick embryos do their bit in the yellow fever vaccine assembly line.*

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The trials and tribulations of the U.S. vaccine industry

U.S. private-sector vaccine manufacturers have not had an easy time trying to exploit their possession of what has been called "one of the most technologically advanced vaccine development and production capabilities in the world."[6]

Their difficulties began in 1972, when the Food and Drug Administration (FDA) took over the regulation of biological products, including vaccines, from the National Institutes of Health (NIH) and very soon called for more demanding safety and efficacy data for registration of vaccines. However justifiable, the move did add to the constraints on industry.

Then, in the late 1970s, increasing public concern and litigiousness over vaccine safety forced manufacturers to invest more heavily in vaccine liability insurance and accept reduced profits from vaccine sales.

Not unexpectedly, the vaccine business began to lose its appeal to many companies. About half of them dropped out of the race, leaving a handful, who remained "as much to meet public health need as out of corporate commitment."[2] Some of these survivors enjoyed a monopoly on supply of certain pædiatric vaccines – Lederle-Praxis for oral polio vaccine, for example, and Merck for the measles-mumps-rubella combination.

But even for these hardy few the battle was far from over.

Some, like Merck, unleashed an onslaught of public protestation and accusations of price gouging, when they announced that their only hope of staying in business and producing the newer more-costly-to-produce vaccines lay in raising prices.

What's more, in the early 1980s, European vaccine manufacturers, eager to take advantage of the worldwide drive to achieve universal childhood immunization, were preparing to conquer international markets by selling huge volumes of vaccines at low prices to UNICEF or directly to developing countries and by boosting their production capacities accordingly. Just as U.S. companies began making plans to join the race, Congress intimated its displeasure over Merck's intention to sell vaccines to UNICEF at prices below those on the U.S. domestic market, thereby in effect putting a damper on any future U.S. industry attempts to penetrate Third World markets.

For Mr Tim Westmoreland, former staff counsel to the U.S. Congress Subcommittee on Health, the original congressional hearing that put the brake on price discounting for vaccines, created a "mistaken belief" that there exists a law or regulation prohibiting the practice. "It's a rumour and it's so widespread that everyone believes it," he told *CVI FORUM*. "It's become an industry paranoia and nobody is doing anything to dispel it."

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Science Phot Library/G. Tompkinson

Step by step *– microprocessor control is part of the pilot-scale production of vaccines for early human trials.*

Whether paranoia, pretext or self-protection, one effect of U.S. manufacturers' reluctance to enter the global vaccine market has been to limit the size and hence cost-efficiency of their production plants. This is a major factor in keeping U.S. vaccine prices far higher than in any other country (DTP, for example, sells at over US$5 a dose on the U.S. private market vs. about US$3-4 on the European private market and oral polio vaccine, which is a monopoly market in the U.S., at about US$10 vs. US$1-2, respectively[1a]).

Certainly, dual or multi-tiered pricing exists, even within the U.S., where since 1982 manufacturers have been selling pædiatric vaccines to the public

sector at prices – negotiated with the Centers for Disease Control and Prevention (CDC) – discounted at between 35% and 80% of private-sector catalogue prices. The problem for industry has been that the proportion of vaccines it sells to the public sector – initially set at about half of all vaccine supplies – gradually increased over the decade 1982-1993. At the same time, its sales to the private sector have brought diminishing profits as a result of volume-based discounting to the increasingly large managed care organizations that now cover about half of the insured population of the U.S.[1a]

To make matters worse for the U.S. vaccine industry, three years ago, Congress enacted a "Vaccines for Children" (VFC) initiative. This offered a new vaccine purchasing mechanism that would entitle needy children (such as those not covered by health insurance – native Americans, Medicaid recipients, etc.) to free vaccines. But by capping vaccine prices at the May 1993 level and raising the proportion of vaccine sold at the lower, public-sector prices – to 78% of doses distributed, according to CDC estimates – the VFC was likely to reduce vaccine industry revenues, at least in the short term.

In their testimony to the U.S. House of Representatives last year, officials of Mercer Management Consulting, a consulting firm hired by the U.S. National Vaccine Program Office to analyse the economics of the U.S. vaccine industry, predicted that the VFC would reduce cash flow through the industry by US$90 to US$120 million a year and funds available for vaccine R & D by US$30 million to US$40 million a year. The VFC, Mercer concluded, "casts a black cloud over the industry [establishing] the Federal government as the driver of the vaccine business [and] ...a near monopsony purchaser."

But clouds, black or white, come and go, and U.S. vaccine manufacturers, buoyed by a biotech industry in full bloom, are nothing if not resilient. Some are even beefing up their production capability in readiness for a surge in demand: Merck, for example, is putting US$150 million into a new facility that executive director Dr Tom Vernon personally hopes "would help make Merck by the year 2000 a contributor to the great vaccine needs of children in the developing world."

By that time, the US industry's 20th century travails may seem in retrospect like growing pains.

five major international conglomerates that together account for nearly 70% of the estimated US$3 billion world turnover in vaccine sales.

Responding to a new reality

To these developments, the private and public sectors responded each in its own way.

Industry, sporting its new, hard-nosed, we-mustn't-forget-the-shareholders look, made the first move. One fine day in 1990, the major European vaccine suppliers announced an imminent hike in the prices of the traditional EPI vaccines.

Was this, as some observers forecast, the end of the alliance? An alliance that had brought universal childhood immunization from dream to near-reality?

No, because the vaccine world was awash with the optimism that the new science and the popularity of vaccines were kindling. That optimism gave birth, in 1990, to the CVI, as a means of bringing *all* the forces at play to bear on the development and introduction of new vaccines. Indeed, one of the CVI's first actions was to set up a task force to examine ways in which industry might collaborate with the CVI's public health objectives.

The mood in the public sector was bullish. "If it does what it was created to do," said Philip Russell, then Special Advisor to the new initiative, "the CVI will speed up the vaccine development process, make it more efficient, and orchestrate the emergence of... vaccines that will prevent most, if not all, of today's preventable child-killing diseases." Dr Russell foresaw only two possible hurdles: "Having enough public sector resources...and ensuring the collaboration of private industry."

Private industry's reaction was mixed – going from upbeat to cautious to frankly sceptical.

"There has been a wind of change,"

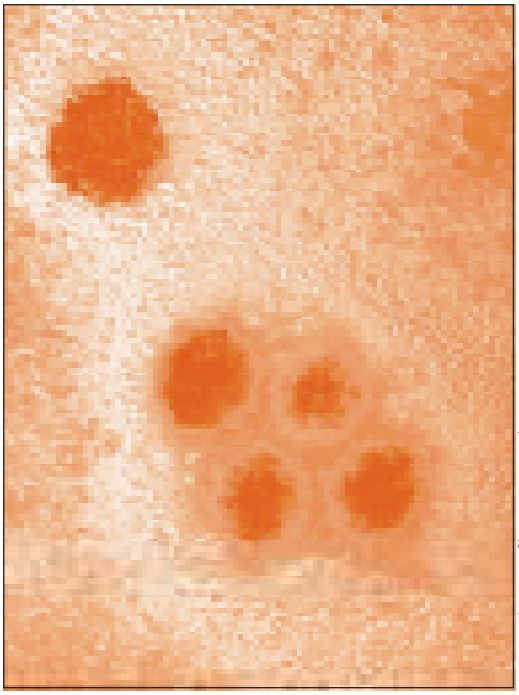
"If it does what it was created to do, the CVI will speed up the vaccine development process, make it more efficient, and orchestrate the emergence of ... vaccines that will prevent most, if not all, of today's preventable child-killing diseases."

"With the advent of the CVI, industry can frankly state its point of view, including financial concerns."

SmithKline's Mr Vandersmissen told *SCIENTIFIC AMERICAN*. Merck's Dr Vernon told the same journal: "It's a major change for a group that has a tendency to denigrate the profit-making sector."

In his keynote address to the 1992 CVI Consultative Group meeting – an annual meeting of CVI collaborators from all sectors of the vaccine community (see *CVI FORUM*, No. 3, February, 1993, pages 4 and 5) – Alain Mérieux, then Chairman of Pasteur Mérieux Sérums et Vaccins, said that because transfer of technology had not been widely successful, only manufacturers in the industrialized world could "assure prompt supplies of large quantities [of vaccine] that meet international standards of quality." But with "all the new constraints on industry" fewer and fewer manufacturers, he said, have the will and resources to do so. He called for "new rules of the game" and a global partnership to overcome the challenges facing industry.

For a gloomier view of those early days, listen to Mr Packer of the Virus Research Institute. "The reaction of industry was: 'This is crazy.' No-one had worked out the most critical factor: Who would pay for vaccines for the world's children, especially as the products and the technology are owned almost exclusively by the for-profit private sector?"



Science Photo Library/London School of Hygiene and Tropical Medicine

Future vaccine target *– dengue hæmorrhagic fever virus may have reason to worry, if vaccine candidates currently in development fulfil their promise (TEM, magnif: 210,000).*

At the end of the first meeting of the CVI's industry task force (officially called *Task Force on Relations with Development Collaborators*), Dr Richard Arnold, task force Chairman and IFPMA vice-president, reiterated the perennial predicament: "The CVI will work if we can find a way of bridging the needs of industry – the only realistic source of the vaccines – with public sector needs."

Back to square one? With industry clamouring for recognition of its needs, of the "true value" of vaccines, of a less "pie-in-the-sky" attitude from the public sector and the public sector clamouring for a less acquisitive attitude from industry? Back to an old deadlock?

No. With the advent of the CVI, the situation had changed. There now was a universally accepted public forum for discussing the sticking points. "Now industry can frankly state its point of view, including financial concerns," said Mr Vandersmissen.

What's more, with its intimation of higher prices to come, industry was, unwittingly perhaps, bringing the issue to a head and forcing the public sector into some innovative thinking that could break the deadlock.

Adapting to the new reality

And indeed, UNICEF and WHO thinkers did put their minds to the problem. They came to the conclusion, as GPV's Amie Batson puts it, "that if we wanted to access new vaccines at affordable prices the atmosphere of mistrust and aloofness between the two sectors just

UNICEF/J. Schytte

Easy does it *– a Mozambican end-user of industry efforts is protected against several diseases thanks to a combination vaccine.*

couldn't go on, that we in the public sector would have to sit down with the industry people and learn their motivations and constraints."

The sitting down together began. And produced, over the past two years, a series of initiatives that are bringing about what many industry and public health experts are hailing as a sea change in public-private sector relations.

But to put more meat into the meetings, to give, as Ms Batson says, an "objective underpinning" to the discussions, in 1993, UNICEF and WHO commissioned a management consulting firm, Mercer Management Consulting, to analyse the vaccine industry and the economics of vaccine production. Presented in January 1994, Mercer's analysis showed that UNICEF's vaccine procurement policy could, at least indirectly, facilitate or hinder the development of new vaccines and public sector access to them and that this policy's traditional emphasis on paying the lowest prices for vaccines was in fact reducing UNICEF's influence on the very companies most able to develop new vaccines. If, Mercer reasoned, UNICEF really wants new vaccines for the world's children, it should use its newly acquired knowledge of industry's needs and motivations to redesign its procurement policy.

Apart from its findings, simply the fact that the Mercer exercise took place had a cathartic effect on relations with private industry. As Terrel Hill, then UNICEF's Principal Advisor for Child Survival, explained to last October's CVI Consultative Group meeting in São Paulo, Brazil, "the study and dialogue with manufacturers made it clear that UNICEF and the immunization community need manufacturers..."

GPV director Dr Jong-Wook Lee saw the study as a real about-face in public sector thinking. "We had kept our distance from industry before. We were afraid we would be contaminated with the profit motive. This study showed we had dropped all that. That we could come down from our ivory tower and do other things than just set vaccination schedules, count missed opportunities and so on. It signaled to industry that we could be practical, analyse pricing structures, do a proper market analysis and gain an understanding of the down-to-earth issues facing the industry and ourselves."

To each according to its wealth

And the ball kept rolling. In November 1994, UNICEF announced a new "vaccine support strategy" that removed another obstacle to fruitful relations with industry. Henceforth, instead of purchasing vaccines – to the tune of US$60 million or more annually – for as many developing countries as expressed the need, UNICEF would in future tie the extent of its assistance to a country to the country's ability – as measured by its wealth and population size – to

"This study signaled to industry that we could be practical, analyse pricing structures, do a proper market analysis and gain an understanding of the down-to-earth issues facing the industry and ourselves."

"In telling them that they should pay and take responsibility for their vaccine supply, the new policy is forcing them to realize that vaccines are of vital importance to them and should be high on their priorities for resource allocation."

*The industry vaccine pipeline at a glance – a sampling**

BIOCINE (ITALY)

- © **Hib oligosaccharide conjugate vaccine (Phase III completed)**
- © **acellular pertussis vaccine (Phase III completed)**
- © **meningococcal A conjugate vaccine for developing countries (Phase II completed)**

CHEIL VACCINE (KOREA)

- © **Japanese encephalitis vaccine (preclinical)**
- © **hantavirus vaccine (preclinical)**
- © **DTaP-Hep-B combination vaccine (preclinical)**

CSL AUSTRALIA

- © **human papilloma virus vaccine (preclinical)**
- © **DTwP-Hep B combination vaccine (in Phase III)**
- © **DTwP-Hep B-Hib combination vaccine (in Phase III)**

MERCK & CO. (USA)

- © **pneumococcal conjugate vaccine against meningitis, pneumonia and otitis media (in Phase III)**
- © **rotavirus vaccine (in Phase II)**
- © **Hep B-Hib combination vaccine (Phase III completed)**
- © **Hep B-Hib-IPV combination vaccine (in planning)**
- © **Hep B-Hib-IPV-DTaP combination vaccine (in planning)**

PASTEUR MERIEUX-CONNAUGHT (FRANCE-CANADA-USA)

- © **DTaP vaccines (Phase III completed)**
- © **DTaP-IPV-Hib combination vaccine (Phase II completed)**
- © **meningococcal A, C conjugate vaccine (in Phase II)**
- © **HIV vaccine (in Phase I/II)**
- © **pneumococcal conjugate vaccine against otitis media (in Phase III)**

SMITHKLINE BEECHAM BIOLOGICALS (BELGIUM)

- © **respiratory syncytial virus vaccine (preclinical)**
- © **DTwP-Hep B combination vaccine (Phase III completed)**
- © **DTwP-Hep B-Hib combination vaccine (Phase III completed)**
- © **recombinant cholera vaccine (preclinical)**

WYETH-LEDERLE (USA)

- © **oral tetravalent rotavirus vaccine (in Phase IIIb)**
- © **pneumococcal conjugate vaccine (in Phase III)**
- © **meningococcal conjugate vaccine (in Phase II/III)**
- © **respiratory syncytial virus vaccine (in Phase I/II)**

** Based on information obtained directly from the manufacturers*

Abbreviations:

DTaP	*diphtheria-tetanus-acellular pertussis combination vaccine*
DTwP	*diphtheria-tetanus-whole-cell pertussis combination vaccine*
Hep B	*hepatitis B vaccine*
Hib	Hæmophilus influenzæ *type b vaccine*
IPV	*injectable poliovirus vaccine*

buy its own vaccines (see *CVI FORUM* No. 10, October 1995, page 10). Some countries would still get some help, commensurate with their potential for self-help. But some would henceforth have to go it alone.

Manufacturers were pleased with the new policy.

Wyeth-Lederle's Dr Hausdorff believes it conveyed an important message to developing countries. "In telling them that they should pay and take responsibility for their vaccine supply, the new policy is forcing them to realize that vaccines are of vital importance to them and should be high on their priorities for resource allocation." Dr Hausdorff blames in part the international public health agencies for the poor image vaccines have historically suffered in the developing world. "In the big push to reach 80% coverage of all children with vaccines, UNICEF and other agencies were very willing to provide vaccines for free to many countries. But how much value will a government official put on something he or she is getting for free or almost free?"

Dr Arnold of the IFPMA agrees, adding that the new UNICEF policy "is clearly moving us out of the old days of penny-a-dose vaccines."

And at Merck, Dr Vernon is "delighted" with the new policy: "It goes a long way to making the demands upon the developed world more clear, more understandable, more justifiable. As long as deeply discounted vaccine was going to countries who can clearly purchase their own vaccine, industry remained sceptical [about public sector intentions]."

Another reason for industry satisfaction with the new policy is that it will no doubt increase the demand for vaccines among developing countries. Already, revolving fund schemes, like UNICEF's Vaccine Independence Initiative and a Pan American Health Organization (PAHO) revolving fund for the Americas, were helping a few countries to become independent of direct procurement assistance and join the ranks of industry clients. UNICEF's new targeted strategy would swell their ranks.

Imaginative bids wanted

Then, last September, as a logical climax to their revamping of the vaccine supply landscape and a way of inviting industry to joint the effort, the UNICEF and WHO vaccine supply experts drafted a new version of UNICEF's biannual vaccine supply tender that broke with tradition in several respects.

This, UNICEF's 1996-1997 tender – more precisely, the Request for Proposals (RFP) section of it – challenged manufacturers to make bids for the supply of new vaccines at prices developing countries could afford. In exchange, UNICEF offered a series of new

Science Photo Library/G. Tomkinson

Unwanted visitors, *like contaminating microbes, are kept out of vials being filled with vaccine thanks to strict sterility procedures.*

"As long as deeply discounted vaccine was going to countries who can clearly purchase their own vaccine, industry remained sceptical [about public sector intentions]."

Enter Africa, Asia, Australia and Latin America

Most of the world's major vaccine manufacturers are concentrated in Europe and North America. But companies elsewhere have been active players on the vaccine supply scene for many years. Some were early participants in research on new vaccines, notably in Japan, where much pioneering work on the Japanese encephalitis, varicella and acellular pertussis vaccines was carried out.

Developing countries, too, have been getting into the world vaccine picture. About ten of them have upgraded or are in the process of upgrading their vaccine production capability and may soon stand ready to compete or join up with some of the world's top-ranking vaccine suppliers.

"More and more developing countries have seriously taken up the challenge to produce their own high-quality vaccine."

"Production of children's vaccines used to be almost entirely in the hands of the industrialized countries," says Dr Isao Arita, President of Japan's Agency for Cooperation in International Health (ACIH) and Chairman of the CVI Task Force on Situation Analysis of Global Vaccine Supply. "Today, with demand for vaccines having increased more than tenfold in the Third World over the past 15 years, more and more developing countries have seriously taken up the challenge to produce their own high-quality vaccine." In terms of sheer volume, developing countries now produce more than 60% of the vaccines they use.

Up-and-coming Third World performers include Brazil, China, India, Indonesia, Korea, Mexico and South Africa.

A few examples:

© In Korea, a number of manufacturers are starting to produce hepatitis B vaccine (Hep B). One of them, Cheil Vaccine, has been supplying a low-cost (plasma-derived) Hep B to immunization programmes in several Third World countries and is currently developing vaccines against Japanese encephalitis and hantavirus and a Hep B-DTaP (diphtheria-tetanus-acellular pertussis) combination. Cheil Vice-President Dr Andrew Towle sees his company "now playing a bigger role in the global vaccine supply."

© In India, the Serum Institute of India Ltd. (SIIL) supplies most of the children's vaccines needed by the national immunization programme, with the exception of polio vaccine and BCG (Bacillus Calmette-Guérin), the anti-tuberculosis vaccine, which it does not manufacture. Through its research wing, Serum Institute of India Research Foundation, the company is developing new vaccines, notably a DTwP (DT-whole-cell pertussis)-Hep B combination, with SmithKline Beecham of Belgium. SIIL Vice-Chairman Dr Jal Mehta says "in India's new climate of liberalization, foreign collaboration is more easily available for co-development of newer techniques and vaccines."

© In Indonesia, BioFarma is the country's sole vaccine producer and with a 103-year history one of the world's oldest. It is now satisfying the country's need for about 200 million doses of the basic pædiatric vaccines, according to its President, Dr Darodjatun. Although state-owned,

UNICEF/J. Sebyrte

Worth waiting for *– parents bring their children in for an immunization session about to begin in a Somali village.*

BioFarma enjoys, he says, "a completely independent management system that is quite free from bureaucratic interference." Its current priorities are to satisfy Indonesia's needs (at least 25 million doses a year) for Hep B and to develop new DTP-based combinations, which it hopes to do through "strategic alliances" with industrialized country manufacturers.

© In South Africa, the government together with the South African Institute for Medical Research has undertaken an in-depth feasibility study. Based on the findings of this study, it is considering combining its three vaccine production facilities – one parastatal, two entirely state-run – into a single commercial company. The government is also considering linking the company somehow to an international vaccine manufacturer. Among the reasons for the overhaul are South Africa's "difficulties in keeping up with the international market in terms of supply, cost and quality," according to Dr Neil Cameron, director of communicable disease control at the Department of Health. "We have also come to realize that our being at one and the same time vaccine producer, regulator, supplier and client results in several major conflicts of interest."

© In Latin America, the Regional Vaccine System (SIREVA) created two years ago is forging ahead with several projects aimed at bolstering the region's vaccine supply. One is a regional network of quality control laboratories, which plans to start quality control training programs. Another is a programme for providing a centralized certification mechanism for DTP producers in the region. Yet another is the promotion of research on vaccines of regional interest: six countries are participating in a study on locally prevalent serotypes of *Streptococcus pneumoniæ* and *Hæmophilus influenzæ* with a view to designing vaccines against these organisms; three countries are collaborating on the development of a conjugated typhoid fever vaccine; and throughout the region several studies are under way on *Neisseria meningitidis* serogroup B vaccines developed in Cuba and Norway.

options. It would, for example, provide private industry with a single buyer for a large market made up of a host of small markets in the poorest developing countries. It would limit supply of low-price vaccines to the neediest countries. It would guarantee long-term (up to four years), large-volume (e.g. up to 3 million doses a month of measles vaccine) purchases of the traditional pædiatric vaccines and the "bundling" of its guaranteed purchase of traditional vaccines to the supply of new vaccines (e.g. Hep B).

The new tender also told manufacturers that each bid would be ranked not just according to price and past performance but according to a range of criteria: How relevant, for example, are its current products to the EPI's immediate priority needs – for oral polio vaccine (OPV), for example, required for the polio eradication initiative currently in full swing, or for the Hep B vaccine that the EPI is struggling to introduce into immunization programmes throughout the developing world or for DTP, which has occasionally been in short supply? And how relevant is a company's portfolio of candidate vaccines further back in the R & D pipeline to UNICEF's, the GPV's and the CVI's priorities for introducing better and new vaccines into developing countries (against diarrhoeal diseases and acute respiratory infections, for example)?

The new tender, said UNICEF's Dr Hill, "signalled to manufacturers that the public sector really did value vaccines even if price is a barrier – not just conceptually but by offering other 'tradables' than price and by asking manufacturers to suggest other forms of value than price." It was "a very practical step forward to developing a closer partnership between public and private sectors."

Industry was, on the whole, delighted. A dozen manufacturers responded, two of them with bids offering a 10% drop in prices (for OPV and the measles vaccine). Others offered to supply several new vaccines for developing country immunization programmes, including monovalent or single-disease vaccines against Hep B, Hib, yellow fever, cholera and typhoid and vaccines linking DTP with the Hep B

"The new tender signalled to manufacturers that the public sector really did value vaccines even if price is a barrier."

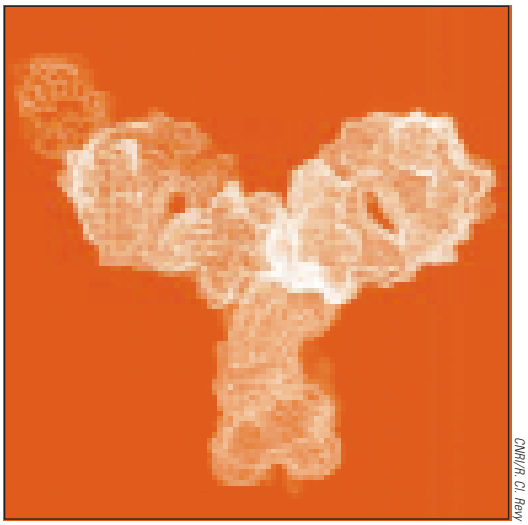
vaccine. Among developing countries qualifying for procurement assistance, demand for just two of these vaccines, Hep B and yellow fever, will amount to 35 million and 14 million doses at a cost of about US$25 million to US$35 million a year, respectively, according to UNICEF estimates. Pasteur Mérieux-Connaught even offered to donate a million doses a year of Hib vaccine for up to four years contingent on a sizable purchase by UNICEF of their DTP.

Commenting on industry's response, Dr Hill said: "The CVI partnership is beginning to yield positive results."

"From the inception of the CVI we have regarded a good working relationship between the public and private sectors as essential."

A new partnership

Today, many vaccine industry executives are clearly upbeat. They certainly have reason to be. The renewed buoyancy and vitality of industry's vaccine development activities is one. In the last decade the number of doses of vaccine used in the world has risen tenfold and the number of diseases that can be prevented by vaccines has doubled – from from 15 to 33.[3] Three new vaccines have been put on the market, Hep B, Hib and Hep A, whose sales in 1993 topped those of all other existing vaccines[4] (Hep B alone, the first vaccine born of the new recombinant gene technology, with annual sales now approaching US$600 million, accounts for 20% of the world vaccine market[4]). In the past 15 years, annual vaccine sales worldwide have soared from US$0.5 billion to about US$3 billion and are expected to exceed US$4.5 billion by the year 2000[1b, 4].



CNRI/R. C. Revy

The heart of the matter *– an immunoglobulin (antibody) molecule of the so-called IgG class latching onto an antigen molecule (top left) from a disease-causing microbe*

Another reason for optimism is what many executives see as a breakthrough in the public-private sector relationship – a breakthrough brought about by the Mercer study together with UNICEF's new vaccine support strategy and tender, and certainly encouraged by the CVI. Today, says the IFPMA's Dr Arnold, "we are now for the first time talking the same language. The public sector generally and the CVI in particular seem to have a greater sense of reality. Overall, the vaccine community seems to be more confident and to have a greater identity of purpose."

Today, Dr Luis Barreto, head of international medical affairs at Pasteur Mérieux-Connaught, believes "we now have a real partnership that is beneficial for all concerned, particularly the children of the world." He sees his job essentially as "working with the WHO, the CVI and the other partners to strengthen that partnership and make it more dynamic, more productive." The future, he adds, is full of hope: "I am really excited about the potential this partnership has for bringing new vaccines, particularly new combinations and new vaccines against acute respiratory diseases, to the people who need them and at prices that are both affordable by those people and motivating to industry." One word of warning: "Don't let's wait too long before doing the epidemiological studies and cost-effectiveness analyses that the introduction of these new vaccines is going to need in developing countries. The longer we wait now, the longer those countries are going to have to wait for the new vaccines."

From the public sector perspective, the GPV's Dr Lee sees "evidence of greater cooperation." Industry, he said, "never really felt the presence of WHO: now it is taking our presence more seriously. And vice versa."

CVI Coordinator Dr Roy Widdus is also enthusiastic. A central CVI goal, he notes, is the speedy introduction of new vaccines into immunization programmes worldwide.

UNICEF/F. Antmann

Promoting the goods *– Peruvian children throw their enthusiasm into an immunization campaign.*

"From the inception of the CVI," he says, "we have regarded a good working relationship between the public and private sectors as essential to achieving that goal. With today's new partnership with industry, our chances of doing so have never been better."

He adds a cautionary note, though: "Current developments are very encouraging but because vaccine development is a lengthy process they should be seen as only a first step in building a better, long-term collaboration between industry and the public sector."

More hurdles to cross

Indeed, a realistic look at today's vaccine scene sees the path to full industry participation in the CVI's objectives still cluttered with obstacles. For example:

© *Disregard of patents in many developing countries* – Francis E. André, SmithKline vice-president and senior medical director, notes that "we have several patents on our hepatitis B vaccine but of the 140 million children born every year, only about 15 million of them are born in countries that respect our patents." The culprits, he said, are principally in Asia and Latin America and "potentially, many countries are involved."

Culprits perhaps, but also victims of their own legal laxity. At the CVI's São Paulo Consultative Group Meeting, Charles M. Caruso, a legal adviser on patents to Merck, pointed out that "without adequate protection for intellectual property in developing countries, there has been no financial or other incentive to devote scarce resources to developing new technology." R & D investment in these countries is thus impeded.

© *The plethora of intellectual property rights (IPRs)* will limit access to new vaccine components developed by the burgeoning biotechnology industry, increase the unit costs of new vaccines and delay their introduction into Third World immunization programmes. The CVI held a workshop on this problem during the São Paulo meeting last October and is continuing to explore, together with industry experts, different possible solutions. They include a "tiered royalty" system for vaccines sold for use in the poorest countries of the world, bulk filling of vaccine by developing countries, and joint private-public venture arrangements.

"We have several patents on our hepatitis B vaccine but of the 140 million children born every year, only about 15 million of them are born in countries that respect our patents."

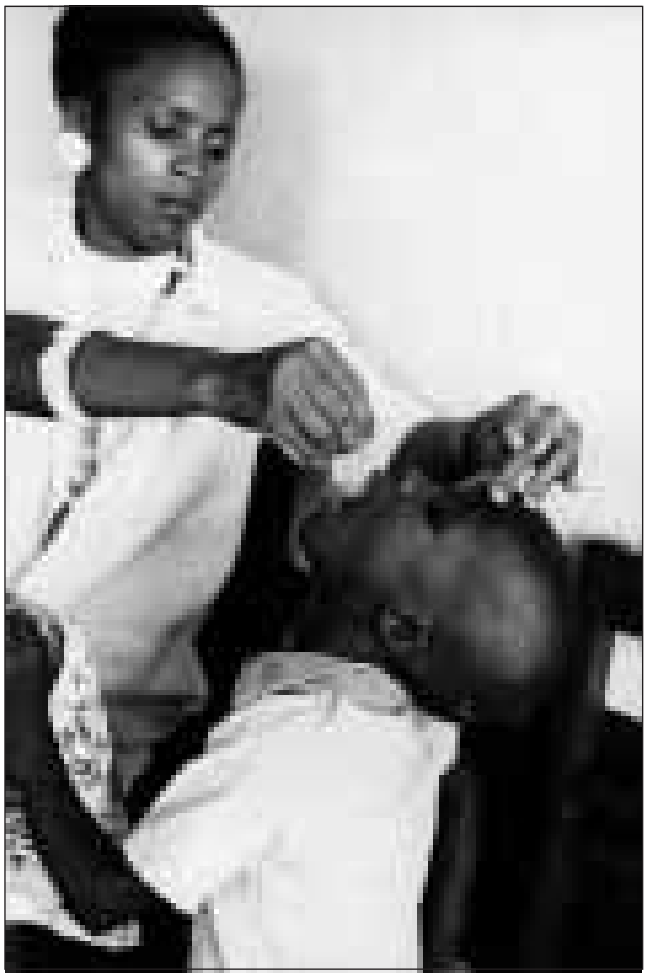
"Clinical trials used for one country are rarely applicable to another and the procedures for obtaining licenses are highly specific to each country's regulatory authority."

© *Lack of universal harmonization of regulatory standards* for vaccine safety and efficacy, notably between the U.S., European and WHO standards. Pharmaceutical firms spend US$350 million a year getting separate approvals from the different European countries, according to one estimate. In 1995, SmithKline Beecham Biologicals, for example, spent "several million U.S. dollars," according to Dr André, on additional clinical trials in order to obtain U.S. registration of its hepatitis A vaccine that had been registered in 1992 in Europe. Efforts are being made – too slowly for some people – to solve the problem.

Conversely, U.S. manufacturers wishing to export vaccines face formidable obstacles. One reason why U.S. suppliers have not exported vaccines more aggressively, according to the Mercer report on the U.S. vaccine industry[1a], is that "separate licensing is required for each country. Clinical trials used for one country are rarely applicable to another and the procedures for obtaining licenses are highly specific to each country's regulatory authority...The present system is costly and discourages vaccine suppliers from obtaining multiple licenses....common regulatory requirements and universal standards for clinical trials that would lead to a more competitive and efficient [U.S.] industry."

On a global scale, the International Conference on Harmonization (ICH), which brings together government officials and industry experts from more than 40 countries in three regions, has finalized "technical guidelines" in 19 of 38 priority topics: only two of the 19 relate to vaccines (both concern "Quality of Biotechnological Products"). A third vaccine-related guideline is still under discussion. Some observers complain that the harmonization process isn't going fast enough. For example, it hasn't, they say, even begun to tackle combinations (see Table, page 22) that link existing vaccines, for which often long-standing regulatory requirements differ from country to country, with new antigens, that should, it is hoped, be fettered by a less heterogeneous, less deeply entrenched regulatory setting.

In Europe, a European Agency for the Evaluation of Medicinal Products (EMEA), established in 1993, began a centralized drug registration system in January 1995 that should speed up the approval process, facilitate free circulation of drugs and vaccines throughout Europe and cut administrative registration costs from more than 250 million Ecus to less than



UNICEF/M. Murray-Lee

What it's all about *– ridding the world of polio drop by drop*

Ian Sriman/Pasteur Mérieux Serums Au

Keeping vaccines safe *from contaminants gives an eery look to a standard industry practice.*

27 million Ecus a year for the different national regulatory authorities combined.

© *Lack of harmonization of immunization policies and schedules.* The problem is particularly acute in Europe, where 47 countries have about as many different vaccination schedules, each vying for first prize in complexity. A recent survey coordinated by the International Children's Centre in Paris found that every European Union country uses a distinctive immunization schedule, each with its different vaccines, different ways of assessing vaccine coverage and different ways of handling private-public sector immunization practices.

Aggravating the problem is the diversity of government control of immunization practices: 12 of the 47 European countries have no compulsory vaccination policies; the remainder have, but for different sets of vaccines. As EMEA chief Fernand Sauer points out, this permutational patchwork situation "create[s] obstacles to free circulation [of vaccines] and prevent[s] manufacturers having access to a continent-wide market."[3] Given the epidemiological similarity of the vaccine-preventable diseases in the European Union, there cannot, Dr Sauer says, be any justification for the diversity. "[The problem] can be solved either by political will or forced by technical developments."

One development already under way is the designing of new combination vaccines with a greater number of antigenic components, which could, he says, make for "simplification of administration... [and solve] the regulatory problems linked to differing vaccination schedules."

© *Potential pitfalls on the road to future combination development.*

Dr Ian Gust, who heads the R & D Division of an Australian national vaccine production facility, CSL Limited, in Melbourne, a major supplier of vaccines to UNICEF, notes that "blending licensed vaccines is neither simple nor straightforward: problems have been encountered with compatibility [and] some crude preparations appear to interfere with the immunogenicity of other components." His firm, he adds, "spent more than two years reformulating the base [DTP] vaccine, which...has left little change from US$8 million, all before the addition of any other antigens."

Dr Michael J. Corbel of the National Institute for Biological Standards and

"This permutational patchwork situation creates obstacles to free circulation of vaccines and prevents manufacturers having access to a continent-wide market."

"Blending licensed vaccines is neither simple nor straightforward: problems have been encountered with compatibility and some crude preparations appear to interfere with the immunogenicity of other components."

Existing and potential combination vaccines

(adapted from a table published by Dr Michael J. Corbel of the National Institute for Biological Standards and Control, Potters Bar, United Kingdom, in* Biologicals, *22, 354, 1994)

"PERTUSSIS" VACCINES

DTP	**DTaP**
DTP-IPV	**DTaP-IPV**
DTP-Hib	**DTaP-Hib**
DTP-Hib-IPV	**DTaP-Hib-IPV**
DTP-Hep B	**DTaP-Hep B**
DTP-Hib-IPV-Hep B	**DTaP-Hib-IPV-Hep B**
DTP-Hib-Men A,C	**DTaP-Hib-Men A,C**

"MENINGITIS" VACCINES

Hib-Men A,C conjugates

Hib-Men A,C,B conjugates

Hib-Men A,C conjugates + B-OMV

Hib-Men A,C B-Tbp

Hib-Men A,C B-OMV-Tbp

Hib-Men A,C B + Pn 6, 9, 14, 18, 19F, 23F (and other possible) conjugates

"OTITIS MEDIA" VACCINES

H-OMP + Pn 6, 14, 19F, 23F (and other possible) conjugates

DTP or DTaP + H-OMP + Pn 6, 14, 19F, 23F (and other possible) conjugates

DTP or DTaP-Hib + H-OMP + Pn 6, 14, 19F, 23F (and other possible) conjugates

"ENTERIC" VACCINES

ETEC-typhoid-rotavirus-Hep A

typhoid-cholera-*Shigella*-ETEC

typhoid-cholera-*Shigella*-ETEC-*Campylobacter*

Campylobacter-Salmonella-Helicobacter

Hep A-Hep B- rotavirus-ETEC

Hep A-Hep B-*Helicobacter*

OTHER COMBINATIONS

Hib-Hep B

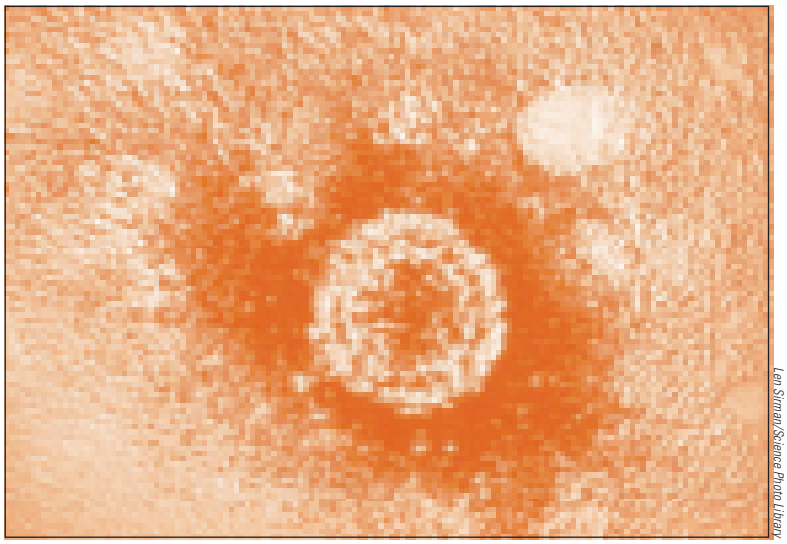
Hep A-Hep B

MMR-varicella

Industry on the whole is gung-ho on combination vaccines. It has good reason to be. Combinations offer a considerable saving of costs on packaging, distribution, marketing and licensing. They are also popular with consumers – particularly managers of immunization programmes, for whom they offer greater convenience (of vaccine delivery), greater compliance (of target population groups), greater coverage (of populations by immunization programmes thanks to greater compliance) and lower costs (of health care thanks to the need for fewer vials, immunization sessions, etc.). Because all four Cs are clearly of critical importance to most Third World immunization programmes, combination vaccines have been called "the point of entry for industrialized country manufacturers to developing world vaccine markets." There is also considerable pressure on the vaccine industry from consumers in developed countries – and hence a strong marketing incentive – to pursue combination vaccine development. Responding to this pressure has been one of the forces driving vaccine companies in developed countries into mergers that offer access to the technology and intellectual property rights needed to produce combinations.

Abbreviations:

aP	*acellular pertussis*	*Hib*	Hæmophilus influenzæ *type b*
DTP	*diphtheria-tetanus-pertussis (whole-cell)*	*IPV*	*injectable polio vaccine*
ETEC	*enterotoxic* Escherichia coli	*Men A, B, C*	*meningococcus serogroup A, B, C*
H-OMP	*non-encapsulated* Hæmophilus influenzæ *outer membrane protein*	*MMR*	*measles-mumps-rubella*
		OMV	*outer membrane vesicles*
Hep A	*hepatitis A*	*Pn*	*pneumococcus*
Hep B	*hepatitis B*	*Tbp*	*transferrin binding protein*



Len Sirman/Science Photo Library

A time bomb *– about 350 million people carry the hepatitis B virus and therefore risk severe, potentially fatal disease: vaccines exist but are not widely enough used.*

Control at Potters Bar in the UK lists some possible technical stumbling blocks to future development of combination vaccines[3]: more and severer side-effects (from greater loads of immunogenic substances or over-stimulation of the immune system, among other factors); reduced immune stimulation (among other things, from "competition" or "interference" between the different antigen components) that may make higher vaccine doses necessary; greater batch-to-batch variation (from complex interaction of multiple components); reduced stability (from chemical degradation processes).

Manufacturers in industrialized countries acknowledge, says Wyeth-Lederle's Dr Hausdorff, "that combination of a given manufacturer's DTP with a new antigen is a surprisingly difficult and empirical process that may require repeated reformulation, testing, not to mention relicensing.[5]"

There could also be regulatory problems. Each new combination must pass tests for the safety, clinical tolerance, immunogenicity and pharmaceutical stability of all its components.

© *The competitive disadvantage of European vis-à-vis American vaccine manufacturers*. European vaccine manufacturers, according to Dr Jean Stéphenne, SmithKline Beecham senior vice-president and general manager, and former president of the European Vaccines Manufacturers (EVM) group, are at a disadvantage over their U.S. counterparts because "the biotech industry has not developed in Europe like it has in North America and that European companies do not necessarily have access to cutting edge biotechnology." One reason for this disparity, he believes, is the greater restrictiveness of European legislation on the use of biotechnology and genetically engineered organisms.[3]

Not too far, not too close

Hurdles and doubts aside, today's vaccine world is without any question not so sharply split into public-private sectors as it used to be. Perhaps we should now talk of zones of interest or intersecting circles. Of a more solid partnership between public health and commercial interests. Of a new relationship in the making.

French psychoanalyst Jacques Lacan once said that a key to a fulfilling human relationship was "finding the right distance" between the partners of a couple. This could also be true of the private-public sector relationship. It is certainly what GPV director Dr Lee believes: "Before, we in the public sector were too far away from industry. We've definitely come closer.

Today's vaccine world is without any question not so sharply split into public-private sectors as it used to be.

UNICEF/S Sprague

Protecting vaccines *from heat damage, thanks to the cold chain, may become a less critical requirement if the CVI and industry can make vaccines more resistant to high temperatures.*

Industry, too, can stop being shy about their main incentive, which is making money. That would help to bridge the gap between us. But we can't come too close. Each side has a role to play in relation to other and each must keep its eyes and mind open to new developments in the relationship. It's all a question of mutual respect."

And finding the right distance.

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