WHO and UNICEF find vaccines too costly

Officials of the World Health Organization (WHO, Geneva) and the United Nations Children's Fund (UNICEF, New York) have pointedly criticized industry and the biomedical research community over vaccine research and pricing policies in a recent comprehensive report on worldwide immunization efforts. Indeed, the report cites the approval of genetically engineered hepatitis B vaccine in 1986 as signaling "that the days of cheap vaccines were over." But both industry representatives and the two global health-care organizations agree that disease prevention programs need to take steps to harness the productive power of commercial biomedicine. "We need more dialogue with industry," says WHO Director General, Hiroshi Nakajima.

The WHO-UNICEF report, "State of the World's Vaccines and Immunization," lauds recent successful campaigns to deliver vaccines against diseases—including polio, measles, neonatal tetanus, diphtheria, pertussis, tuberculosis, hepatitis B, and yellow fever—to the world's children, particularly in developing countries. But the report also warns that, "unless the international community continues to back scientific research and global immunization with adequate resources for new vaccines. . .the great promise of molecular biology and genetic engineering may be squandered."

High on the list of global vaccination campaigns are efforts to eradicate polio—a goal that officials expect to meet by the year 2000. In 1995, for instance, nearly half of all children under five, some 300 million, received supplementary doses of polio vaccines during special national immunization days. But even here, officials are concerned over budget "shortfalls," mainly from decreased donor funding, that now have the managers of this campaign scrambling for the $600–800 million needed for vaccine purchases, personnel, training, research, logistics, establishment of a cold chain to preserve vaccine activity, and development of a global laboratory network. The current full allotment of six childhood vaccines (against polio, diphtheria, pertussis, tetanus, measles, and tuberculosis) now costs less than $1 for the vaccines—plus $14 for program costs.

The hepatitis B vaccine has been a touchstone for the vaccine cost discussion. Nakajima points out that the cost of the recombinant hepatitis B vaccine has been dropping, in part because several countries in the developing world, including China, Korea, and Cuba, now are manufacturing the product and making it widely available. However, he adds, unless its price falls below $1 per dose, this vaccine remains out of reach for much of the world. "We're not saying all vaccines should be free," says Carol Bellamy, executive director of UNICEF. "We're hoping for a healthy, competitive market and to create a varied pricing structure."

But Thomas Bombelles, who specializes in international issues for the Pharmaceutical Research and Manufacturers of America Association (PhRMA, Washington, DC), argues that innovation can be expensive. "The development costs for vaccines are not all that much lower than for drugs," he says. "R&D for vaccines is often on the lower end of the range for pharmaceutical products, but it can be from $50–350 million, which is still an awful lot of money, and there has to be a reasonable return on such development costs." In any case, he says, "The cost is actually very small." Even though its price is higher than that of older vaccine products, its effectiveness makes it a "fantastic bargain" when health outcomes are considered, he says.

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

Child receiving an oral polio vaccine in a hospital in Phnom Penh, Cambodia.

Other improved recombinant vaccine products are nearing regulatory review. For instance, Chiron Corporation (Emeryville, CA) announced in October that it is seeking regulatory clearance for the marketing of Pertugen, a diphtheria, tetanus, and genetically engineered acellular pertussis (DTaP) vaccine for infants and children. Pertugen is the first recombinant DTaP vaccine to detoxify the pertussis toxin.

Pricing is not the only impediment to wider vaccine development and usage. Bombelles notes that adequate safeguards for intellectual property rights are crucial. Strengthening of intellectual property laws in China, he says, made it easier for Merck (Whitehouse Station, NJ) to share some of its hepatitis B vaccine know-how with Chinese collaborators, enabling them to build up domestic vaccine manufacturing capacity.

Another issue pivots on health-care priorities in developing countries. With more than 300 candidate vaccines "in the pipeline," developing countries "need to make resources available at the national level," points out Ciro de Quadros, Nakajima's special advisor for the WHO Global Program for Vaccines and Immunization. Institutions in such countries need to form "consortia to bring vaccine prices down and make sure these products are widely used."

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Edible plant vaccines

The first human clinical trial for an edible, plant-based vaccine could start at the beginning of 1997. A team headed by Charles Arntzen at the Boyce Thompson Institute for Plant Research (BTI, Ithaca, NY) is currently undertaking advanced preclinical research on a vaccine for diarrhea that consists of raw transgenic potatoes expressing an *Escherichia coli* enterotoxin LT-B subunit gene. If the work goes as planned, the vaccine could enter clinical trials on 12 volunteers at the Baltimore Vaccine Testing Center (Baltimore, MD) in the new year. The potato vaccine, may, however, be beaten to the market by more palatable or technically accessible alternatives.

Arntzen's research and the similar work of Hilary Koprowski's group at Thomas Jefferson University (Philadelphia, PA) on plants that produce rabies and human immunodeficiency virus antigens are directed at producing edible vaccines for developing countries. "How would you expect [people in] Africa or Asia to be vaccinated except by the oral route?" asks Koprowski. Plants are "the cheapest and the most accessible production method," he says, and they eliminate both the need for refrigeration, needles, and trained medical staff, and the risks of pathogen-derived vaccines.

The BTI potato vaccine has been shown to stimulate the production of specific antienterotoxin IgG and IgA in mice. The next preclinical hurdle for the vaccine is to show that it can protect mice against challenge with the *E. coli* toxin, or with *E. coli* itself.

Even though the potato vaccine will be the first plant-based vaccine in human trials, it is still really just a model system. Few people enjoy raw potatoes (although Charles Arntzen did as a child, he told *Nature Biotechnology*). According to Arntzen's colleague, Hugh Mason, the first commercial edible plant vaccine will be in bananas. They are much more palatable,

US Bioethics Commission meets, outlines agenda

Meeting for the first time in October, members of the US National Bioethics Advisory Commission (NBAC, Washington, DC) established a spirit of cordial informality and gingerly avoided becoming bogged down by peculiar technicalities of federal conflict-of-interest rules. They also took modest steps to shape an agenda to consider over the next few years of regular meetings. The annual operating budget for the commission will rise from the current $500,000 to the eventual target of $1–2 million, according to chairman Harold Shapiro, who is president of Princeton University (Princeton, NJ).

NBAC members appear to be slating several issues of importance to the biotechnology industry for near-term consideration, including the use of human subjects in biomedical research, genetic privacy and related tissue sample usage issues, and possibly gene patenting.

No single issue drew more attention than concerns with the overall operation of institutional review boards (IRBs)—the sprawling, locally operating but federally sanctioned, system for reviewing biomedical research protocols and protecting the rights of human subjects. The US National Institutes of Health (NIH, Bethesda, MD) oversees this system, requiring institutions that receive federal funds for research to abide by certain minimal standards for establishing and maintaining IRBs. Although a national interagency group broadly reviews IRB performance and policies, in practical terms the Office for Protection from Research Risks (OPRR) within NIH takes the lead in dealing with IRBs.

Members of US National Bioethics Advisory Commission: (From left to right) back row, T.H. Murray, L.H. Miike, E.J. Emanuel, B. Lo, S.H. Holtzman, E.J. Cassell, A.M. Capron; second row, J.Childress, B.O. Kramer, D.R. Cox, R.G. Dumas, L.M. Flynn, P. Backlar; front row, R.H. Charo, A. Brito, H.T. Shapiro, D. Scott-Jones.

Despite a good performance record, there are shortcomings to the IRB system that reflect the way it was established and affect the way it performs. "In 1996, we don't have the tools to protect all human subjects," points out OPRR director Gary Ellis. There is no federal statute applicable to such research, meaning current rules do not apply universally. Moreover, the IRB system is far from uniform—a factor that sometimes proves frustrating or worse for investigators conducting multisite clinical trials.

Francis Collins, director of the NIH National Center for Human Genome Research, has urged NBAC members to put genetic privacy issues high on their agenda. As data associating specific diseases with molecular-level genetics continues to accumulate, he says, the potential for abuses by insurers and employers also grows. "One of the most troubling issues is healthy persons with genetic information that may be predictive of a disease," he says. Another narrower, but more immediate, issue revolves around the future use of DNA-containing tissue specimens now held by pathologists; unauthorized testing of such samples also could lead to abuses. Hence, he says, strong NBAC recommendations in these areas would be welcome.

Representatives from the biotechnology industry agree that genetic testing information should be protected from abuse. However, in calling for a "flexible regulatory framework," Suzanne Tomlinson from the Biotechnology Industry Organization (BIO, Washington, DC) recommends that Congress not single out genetic testing technology but, instead, "pass a comprehensive medical privacy bill that includes protections for genetic privacy."

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especially for children, and are a staple crop in developing countries. The BTI has recently received a three-year foundation grant from the Rockefeller Foundation (New York) to set up links with researchers at the Centro de Investigacion y de Estudios Avanzados del IPN (CINESTAV, Mexico City) to develop the banana transformation system and maximize LT-B expression levels in transformed bananas.

Other researchers see a fundamental disadvantage with the banana system: They regenerate only slowly. It could be two years at least, for instance, before BTI can evaluate the antigen levels in its banana transformants. Consequently, Koprowski is using transgenic tomatoes and alfalfa—plants in which expression levels can readily be assessed within months—for his rabies and HIV vaccines. Faster still is another of the Jefferson group's approaches: the use of plant viral vectors that express the antigen gene to infect plants. Using this method, researchers can optimize antigen production level in days.

The BTI potato vaccine, which stimulates the production of antientertoxin IgG and IgA in mice.

The plant virus method is also being developed by Axis Genetics (Cambridge, UK). Axis' most advanced project involves an animal vaccine: Injecting mink with extracts of plants infected with a cowpea mosaic virus that expresses a mink enteritis antigen gene protects the animal against subsequent virus challenge, according to CEO Iain Cubitt. The next phase for Axis will be to demonstrate the efficacy of vaccines administered orally as plant material, a milestone Cubitt expects to pass "within the next year." Neither the enteritis vaccine nor a parvovirus vaccine that Axis is developing as part of an European Union-funded program have yet been administered through the oral route.

Despite these more rapid methods, the BTI trial remains of considerable significance as a proof of principle. "Everyone is waiting for us to actually prove that this works," says Charles Arntzen. The first trials next April, however, will not resolve this completely. Although the volunteers will be tested for altered immunological status, they will not be challenged with the *E. coli* toxin.

Emma Johnson