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Wendy K. Mariner
Boston University School of Law

Robert C. Gallo

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Recommended Citation

Wendy K. Mariner & Robert C. Gallo, *Getting to Market: The Scientific and Legal Climate for Developing an AIDS Vaccine* , *in* 15 Law, Medicine & Health Care 17 (1987).
Available at: https://doi.org/https://doi.org/10.1111/j.1748-720X.1987.tb01004.x

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Bluebook 21st ed.
Wendy K. Mariner & Robert C. Gallo, Getting to Market: The Scientific and Legal Climate for Developing and AIDS Vaccine, 15 L. MED. & HEALTH CARE 17 (1987).

ALWD 7th ed.
Wendy K. Mariner & Robert C. Gallo, Getting to Market: The Scientific and Legal Climate for Developing and AIDS Vaccine, 15 L. Med. & Health Care 17 (1987).

APA 7th ed.
Mariner, W. K., & Gallo, R. C. (1987). Getting to market: the scientific and legal climate for developing and aids vaccine. Law, Medicine and Health Care, 15(Issues 1-2), 17-26.

Chicago 17th ed.
Wendy K. Mariner; Robert C. Gallo, "Getting to Market: The Scientific and Legal Climate for Developing and AIDS Vaccine," Law, Medicine and Health Care 15, no. Issues 1-2 (Summer 1987): 17-26

McGill Guide 9th ed.
Wendy K. Mariner & Robert C. Gallo, "Getting to Market: The Scientific and Legal Climate for Developing and AIDS Vaccine" (1987) 15:Issues 1-2 L Med & Health Care 17.

AGLC 4th ed.
Wendy K. Mariner and Robert C. Gallo, 'Getting to Market: The Scientific and Legal Climate for Developing and AIDS Vaccine' (1987) 15(Issues 1-2) Law, Medicine and Health Care 17

MLA 9th ed.
Mariner, Wendy K., and Robert C. Gallo. "Getting to Market: The Scientific and Legal Climate for Developing and AIDS Vaccine." Law, Medicine and Health Care, vol. 15, no. Issues 1-2, Summer 1987, pp. 17-26. HeinOnline.

OSCOLA 4th ed.
Wendy K. Mariner & Robert C. Gallo, 'Getting to Market: The Scientific and Legal Climate for Developing and AIDS Vaccine' (1987) 15 L Med & Health Care 17
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Getting to Market: The Scientific and Legal Climate for Developing an AIDS Vaccine*

Wendy K. Mariner and Robert C. Gallo

Expectations of a vaccine to prevent acquired immunodeficiency syndrome (AIDS) are rising. Not only are the prospects for an effective immunogen improving, but immunization appears to hold the greatest promise for halting the spread of infection and disease.[1] Identification of the causal agent—the retrovirus called HTLV-III, LAV, or generically, HIV (human immunodeficiency virus)—has provided the direction and limited the options for containing the disease.

Prevention is, of course, critical where the disease must be presumed to be fatal in all cases. Although there is no clear evidence that any single exposure to HIV will result in infection or disease, prudence dictates that all exposures be considered potentially infectious and, ultimately, disease-producing until more is known.[2] Public education or, more specifically, behavior modification, intended to reduce or eliminate unsafe sexual contact and the sharing of syringes and needles by users of illicit intravenous (IV) drugs, is perhaps the only effective means of prevention that currently exists.[3] Public education, however, has rarely been sufficiently persuasive to *eliminate* the transmission of infectious disease, and faces distinct resistance when applied to matters of sexual conduct and illegal drug use.[4] Therefore, while education is necessary, it may not be sufficient to reduce the risk of exposure to HIV to the level required for damping out the spread of infection.[5]

Yet vaccine development faces obstacles as significant as those confronting a successful program of public education. The scientific and technical hurdles are themselves formidable. But while the scientific task is becoming clearer, legal and ethical concerns are beginning to loom larger. Among the questions that have yet to be answered is whether producers of any AIDS vaccine will be or should be held liable for the probably inevitable adverse reactions to the vaccine. If so, will the threat of liability dissuade commercial producers from seeking to develop or distribute a vaccine? If not, will the public be confident that the vaccine is safe enough to use? Are Food and Drug Administration (FDA) requirements for testing and licensing sufficient to ensure a safe and effective vaccine? Should they be relaxed to speed a promising vaccine to market or should they be rigorously enforced to keep a potentially dangerous one out of circulation?

Answering these questions requires a clear understanding of the scientific, legal, ethical, and public policy issues at stake and, most importantly, their interdependence This article attempts to clarify such issues and to indicate how they may affect both private and public decisions to produce, distribute, and accept a vaccine.

Scientific Approaches to Vaccine Development

At least seven types of vaccine preparations are under study, some with practical promise, others with more theoretical prospects at present. They include the use of nonpathogenic infectious HIV, killed HIV, purified natural virus proteins or subunits, genetically engineered subunit proteins and synthetic peptides, infectious recombinant viruses, and anti-idiotypes.[6]

The nature of HIV and the apparent severity of the resulting disease limit the possible types of vaccines that could effectively prevent infection. Because AIDS must be presumed fatal in essentially all cases, a vaccine must carry no risk of causing HIV infection. This rules out inactivated

*The authors gratefully acknowledge the assistance of Ann H. Sliski, D.Sc., of the National Cancer Institute, in the preparation of this article.

or attenuated vaccines made with purified live virus as first choices since they carry a risk, however small, of containing live, pathogenic virus. Even if the immediate pathogenic effects are eliminated, however, an attenuated virus presents an additional risk of inducing cancer long after vaccination. HIV shares certain features of its genetic structure with other cancer-causing viruses that, when integrated with host-cell DNA, "turn on" cellular genes. The aberrant expression of these genes may lead to cancer. Killed HIV may also have limited efficacy, as do other killed retroviruses. Kittens immunized with inactivated feline leukemia virus, for example, have been reported to show lower levels of immunity when challenged than do controls.[7]

The most promising approach to vaccine development involves the use of a purified HIV protein. If selected carefully, the protein should present no risk of HIV infection and little risk of secondary effects. However, the selection is not a simple matter. For an effective vaccine, two types of immune response are sought: neutralizing antibodies (to prevent establishment of the virus) and a T-cell immune response (to prevent the action of virus-infected cells).

Neutralizing antibodies attack particular regions of the virus' envelope glycoprotein, the part of the surface of the virus that is most exposed to the immune system.[8] The antibodies prevent infection of a cell by interfering with virus penetration of the cell membrane. Thus a critical research question is whether human beings can develop the necessary response that prevents the virus from infecting the cell. While persons infected with HIV have been found to develop antibodies to the envelope, not all antibodies have succeeded in interacting with the virus envelope in a way that actually prevents infection.

Complicating both the development and the testing of potential immunogens is the uncertain significance of the immune response in human beings. While persons infected with HIV develop a strong humoral immune response,[9] the existence of antibody does not necessarily correlate with protection from disease. Neutralizing antibody has been found even in late-stage cases of AIDS.[10] It is thought that some form of immunity must exist, since a large number of persons presumably exposed to HIV have neither become infected nor developed AIDS. It remains unclear whether the development of neutralizing antibodies is sufficient protection against disease. Ordinarily, the viral RNA of retroviruses makes a double strand of proviral DNA that integrates into the DNA of the host's cells and is replicated with it. It is possible that the virus is transmitted from cell to cell, as well as directly by the free virus itself. If so, full protection would entail blocking the process of infection between cells, by producing either cytotoxic antibodies to eliminate infected cells or a cell-mediated immune response directed against infected cells.

Another possible explanation for the discrepancy between the presence of antibody and disease arises from the complexity of HIV itself. HIV includes not merely a few different strains but a broad continuum of related retroviruses. The viral genome has about 9,500 nucleotides; the number of nucleotide differences found between isolates ranges from 80 to over 1,000.[11] Thus an effective vaccine must produce a broadly reactive response to the vast number of possible "strains" or "substrains" that might infect someone.

Considerable research now focuses on whether the necessary broad response can be achieved using purified envelope or fragments of envelope. Envelope variability makes it difficult to know whether one preparation will protect against a different substrain with a different envelope.[12] It may be necessary to immunize with a "cocktail" of different envelope fragments to achieve a protective response.[13] To simplify the collection of envelope fragments, the possibility of common conserved regions of envelopes in different substrains is being studied.[14]

Given the variability of HIV envelope, the risks of using attenuated live virus, and the need to produce large quantities of safe vaccine, research is leaning toward molecular engineering. Recombinant techniques simplify and speed up the process of collecting the desired virus proteins, and they do not require expensive animal-cell subculture to grow the virus. The feasibility of recombinant vaccines, however, may depend upon whether carbohydrate helps or inhibits the induction of neutralizing antibodies.[15] The HIV envelope is covered by an unusual amount of carbohydrate (glycosylation),[16] which might protect it from attack by antibodies.

Some research has tested promising techniques for obtaining envelope glycoprotein to produce neutralizing antibodies. This entails inserting the HIV surface antigen gene, or a synthetic peptide, into yeast or bacteria that are capable of expressing it in large quantities.[17] For example, success has been achieved in expressing the envelope using vaccinia virus,[18] and fragments of the envelope using Escherichia coli.[19] The gene product is then collected and mixed with adjuvants to prepare a vaccine. Goats immunized with the preparations have developed antibodies equivalent to those produced using natural envelope protein (gp 120) as immunogen.[20] Since the bacteria have no carbohydrate coating, the experiments also indicate that glycosylation is not necessary to produce neutralizing antibody, so that recombinant materials may hold real promise as a means of producing immunogens.

Recombinant techniques can also be used to piggyback the HIV surface antigen onto a safer infectious virus. The desired gene has been incorporated into vaccinia virus, for example, which then produces a carefully altered antigen as it replicates normally. However, in the United States, using vaccinia virus as the vector would first entail immunizing the population against vaccinia, and the

vaccinia itself causes infection in some individuals. The Advisory Committee on Infectious Disease has already recommended against using live vaccines of any kind in persons with clinically apparent AIDS.[21] The recent death of a young man who developed disseminated vaccinia and AIDS after receiving multiple vaccinations during basic military training raises questions about using live vaccines in persons with subacute HIV infection and T-cell deficiency.[22] Therefore, other viruses, such as nonpathogenic strains of herpes and adenoviruses, are being considered. An advantage of this type of recombinant virus vaccine is that once the prototype is developed, batches of vaccine could be produced and delivered inexpensively, in essentially the same way as other vaccines currently in use.

Other approaches to vaccine development are more experimental at present. One is the anti-idiotypic antibody that mimics an epitope on the natural virus itself. It appears that it would be necessary to vaccinate initially with a neutralizing monoclonal antibody so that this initial antibody would produce a mirror image of itself—the anti-idiotype—to spur the development of protective antibodies. Although this approach would present a safe preparation,[23] it will surely be years before the correct monoclonal antibody is developed, if at all. Another experimental approach is that of preparing subunit vaccines by molecular mimicry. In theory, X-ray crystallography could be used to make a three-dimensional design of the surface of the virus. Amino acids could then be selected to "build" a reproduction of the relevant surface structure, which would artificially provoke the desired immune response.

It seems possible, in principle, to solve the problems of identifying techniques for producing HIV antigen and attaching antibodies to the antigen so as to prevent its disease-producing mechanism. The attractiveness of different approaches, of course, will depend upon the extent to which they can produce large quantities of vaccine with no significant dangers at a reasonable cost. The most formidable barriers to scientific success appear to be (1) isolating sufficient antigenic variants to produce a wide-ranging immune response that protects against the multiple substrains of HIV, and (2) confirming their effectiveness by means other than antibody titer. The first may be complicated by genetic shift and drift. The second may mean that it will take longer to test the vaccine than it will to develop it in the first place. At present most progress has been made in the recombinant virus vaccine approaches. The research community has a relatively clear picture of possible approaches to developing vaccines and of the steps required to identify which, if any, of these can be successful. This does not mean that the task is a simple one or that it will actually result in an effective vaccine. Rather, it means that we have our work cut out for us. Thus it is all the more important that we avoid erecting significant new obstacles to an effective vaccine.

Testing Vaccines

While the prospects for developing *promising* immunogens are good, identifying those that can actually provide an immune response protective against AIDS is problematic. Here the technical problems are compounded by the FDA's requirements for licensing vaccines. Ideally, the FDA's regulations ensure that a vaccine produces the intended immunity against disease by requiring a demonstration of its safety, purity, and potency.[24] Like pharmaceuticals, vaccines must be tested in vitro and in animals before being tested on human subjects.[25] The testing sequence and methodology contemplated by the regulations ordinarily permit a scientifically credible assessment of the safety and efficacy of a vaccine. But HIV is not an ordinary virus.

It may be difficult to conduct the normal tests or to obtain reliable evaluations of candidate vaccines under existing regulations, unless testing continues for many years. Yet the need for new or lengthy evaluation methods conflicts sharply with the urgent need to produce an immunizing agent to prevent a disease as deadly as AIDS. If science is unable to reconcile these objectives, we may face an ugly dilemma: delay distribution of perhaps the only effective defense against AIDS and thereby fail to prevent untold numbers of deaths, or prematurely introduce a vaccine that might itself contribute to the spread of disease.

To further complicate the picture, the choice will undoubtedly be influenced by vaccine developers' fears of liability for adverse reactions to vaccines—which tend to favor extensive testing—and their desire for patent protection and the economic rewards of marketing the first vaccine—which tend to favor early release.

A major concern at present is whether any candidate vaccine is ready to be tested in human beings. While few immunogens have been fully tested in animals, it is unclear whether extensive animal trials will be cost-effective. Chimpanzees are the only species that can be regularly infected with HIV, and thus can serve to test the development of antibodies against HIV infection.[26] Rhesus monkeys have been infected with HIV and have produced antibodies, but too infrequently to serve as a reliable model for the immune response in humans. Chimpanzees produce antibodies and shed virus in much the same way as do human beings. They have manifested lymphadenopathy and temporary T_4 depression but have not yet developed clinically observable AIDS. Thus they are being used to test the possibility of inducing appropriate neutralizing antibodies and then are being challenged with the HIV virus to determine whether infection is prevented.

Since a variety of immunogens and routes of inoculation might be tried, a large number of chimpanzees may be needed. Chimpanzees, however, are scarce and expensive "resources." One way to minimize the use of

chimpanzees themselves is to test the effect of induced chimpanzee antibodies on different HIV variants in vitro. While cost appears to be a major concern in some quarters, it seems that the number of animals is the more serious constraint. Of course, there are ethical objections to the use of chimpanzees as test subjects, but such concerns are not confined to testing AIDS vaccines.[27] Here, the choice may be between testing chimpanzees and testing human beings. Given the potential risks of challenging any subject with HIV, such ethical arguments are not likely to be persuasive. But while chimpanzees simulate the human immune response in the production of antibodies, there is no exact animal model for the development of disease itself. Therefore, it remains unclear if chimpanzees can be used to tell us whether a candidate vaccine is in fact effective in preventing disease.

Another problem in animal vaccine trials involves the length of time between infection with HIV and the development of disease. It seems clear that HIV, unlike better-known viruses for which vaccines exist, such as the hepatitis B virus, may not produce the debilitating effects of AIDS, or even AIDS-related complex (ARC), for many years after initial infection.[28] The problem is, of course, that we do not yet know precisely how long it takes for disease to develop, or whether it may never develop in some systems. Therefore, we do not know how long to wait after challenge to determine whether immunity has been established. The idea of waiting five years after challenge to assess the effectiveness of a candidate vaccine may be politically intolerable. Yet it may be impossible to determine whether an initial immune response endures throughout the desired period if the probability of actual infection absent vaccine-induced immunity is low.

Already there are calls to bypass animal trials and go directly to clinical trials in human beings. But human subjects pose equally difficult problems. A threshold question is defining the population to serve as test subjects. Typically, vaccine trials have involved healthy volunteers. Ensuring a subject population free from existing infection would require screening for HIV. But those who demonstrate seronegativity on initial screening may not in fact be free from infection. The subjects would have to be screened again at a later date before vaccination, thus delaying the trials for several months. The population might also need to be monitored for lack of exposure to the virus during the waiting period, which could be time-consuming and expensive, not to mention intrusive; the alternative of self-reports of behavior may not be sufficiently reliable.

The likely success of attracting volunteers in the United States to serve as subjects also remains open to question. If initial trials focus on high-risk populations, the mere fact of participation could identify volunteers as homosexuals or IV drug abusers, with possibly detrimental effects on their employment, insurance coverage, and social life. While clinical trials must maintain the confidentiality of subjects, it may be difficult for volunteers to avoid detection if they have a lengthy period of interaction with investigators. High-risk populations, however, may not prove the best source of volunteers, especially if, as in San Francisco and New York, those groups already have a high prevalence of infection.[29]

A related problem arises in testing vaccines outside the United States. Although FDA regulations now make it easier to rely on foreign trials as some evidence of product safety and effectiveness, it is often difficult to determine whether the results of such trials would apply to United States populations. For example, the high rate of HIV infection in parts of Africa may make it difficult to find healthy volunteers. If there is a high prevalence of subclinical infection, vaccines using infectious recombinant viruses, such as the vaccinia-based vaccines, may produce additional disease in a vulnerable population. The trials could conceivably provide evidence that the vaccine has no protective effect, even though it could prevent disease in most Americans, who are not subject to multiple infections. Alternatively, the trials might suggest a degree of effectiveness that could not be achieved in the United States. Although the need to stop the spread of disease may induce some governments to encourage vaccine trials in their nations, whether and how they should be done remains a matter of debate.

Finally, perhaps the thorniest problem is that of designing clinical trials so as to demonstrate whether the vaccine tested is in fact safe and effective. A double-blind format is generally preferred, but it may be impossible to maintain blindness. Participants may decide to be screened at an unrelated clinic. If their tests show a positive antibody response, they may presume themselves to be in the group that received the vaccine. They might then engage in unsafe sex or drug abuse and increase their risk of exposure to the virus, assuming that they are protected against infection. Those who discover that they are in the control group may be especially careful to avoid exposure. In such circumstances, the trials could conceivably result in the vaccinated group showing higher rates of infection than the controls.

Of course, it is also possible that *all* participants in clinical trials will cease or reduce unsafe behavior. After all, investigators have an ethical and legal obligation to advise volunteers how to protect themselves against infection. Here again, it may be difficult to isolate the effect, if any, of the vaccine on the resulting rates of infection. A lower incidence of infection among vaccinated persons might also be explained by safer behavior resulting from better education. Even if the vaccine is the source of protection, it might take years of testing to determine how long immunity lasts. Thus it remains to be seen just how we can determine whether a vaccine is in fact effective, and if so, in what dosage and for how long.

The safety of a vaccine is likely to remain in question

even after it has been licensed and distributed. Adverse reactions may not be discovered even in the most carefully constructed clinical trials. Since such trials typically involve only a few thousand participants, reactions that occur as rarely as once in 100,000 or 1,000,000 vaccinations are not likely to be seen during premarketing tests. But they may manifest themselves once the vaccine is in regular use nationwide, with unfortunate consequences for all.

Tort Liability for Vaccine-Related Injury

The scientific and ethical issues surrounding the testing of candidate vaccines are complicated by uncertainty about the potential liability for adverse reactions to any such vaccine. The uncertainty is twofold: uncertainty as to the legal principles that will be applied if a vaccine injures or is thought to injure any recipient and uncertainty as to what legal principles *ought* to apply in such a case. This concern undoubtedly stems from recognition that adverse reactions are sure to follow vaccination with AIDS vaccine—if not during clinical trials, then after a licensed vaccine is marketed.

Producers and manufacturers of vaccines may be held liable for injuries resulting from their products in strict liability[30] or in negligence.[31] Strict liability is imposed when the product has a defect that renders it unreasonably dangerous, as measured by the expectations of the vaccine recipient or consumer.[32] Three categories of defects may give rise to strict liability: manufacturing flaws,[33] defects in design,[34] and inadequate directions for use or warnings of risks.[35] A manufacturer may be held liable for negligence when it failed to exercise the appropriate level of care required of it in producing the product and, as a result, the product caused actual injury.

Liability for failing to provide an adequate warning of vaccine risks has a long and controversial history.[36] However, in view of the somewhat greater ease of avoiding liability on this ground and its limited effect on decisions concerning what type of vaccine to produce, it will not be considered here.

For years vaccines were thought to be exempt from strict liability for design defects and liability for negligence in design, but that assumption has been soundly criticized, most recently in the *Toner v. Lederle Laboratories* decision by the Supreme Court of Idaho in February 1987.[37] These decisions raise the possibility of subjecting vaccine manufacturers to liability for injury resulting from defects in vaccine design on the grounds that the risks associated with the vaccine could have been avoided had a different vaccine been produced. This has caused concern among prospective vaccine producers that their financial exposure for possibly unforeseeable adverse reactions may outweigh their potential revenues from marketing the vaccine.[38]

Potential liability for design defects can influence decisions about what types of immunogens ought to be studied, the duration of animal and clinical trials, the population targeted to test immunogens in clinical trials, whether to seek FDA approval of a candidate vaccine, and whether and how to market and monitor a licensed vaccine. The concern is that the pressure to produce a vaccine against AIDS will result in a vaccine that might not be optimal, in the sense of being free of all possible risks, because there is too little time to investigate or discover unforeseeable or even some foreseeable reactions. The fear of liability for defects in design may inhibit manufacturers from experimenting with some immunogens or from attempting to develop any at all. Even the FDA is concerned about such liability, both because it might affect prospective vaccine producers and because it might implicate the FDA itself among those responsible for releasing a dangerous vaccine.

The brief history of this theory of liability for vaccine-related injuries, however, argues against the likelihood that a new vaccine against AIDS would be found to have an actionable defect in design. In vaccine cases, strict liability has been defined in terms of its formulation in sec. 402A of the Restatement (Second) of Torts. In pertinent part, that section states:

> One who sells any product in a defective condition unreasonably dangerous to the user or consumer . . . is subject to liability for physical harm thereby caused to the ultimate user or consumer. . . . [Even if] the seller has exercised all possible care in the preparation and sale of his product.[39]

For the most part, risks inherent in properly prepared vaccines have not been considered to render a vaccine either "defective"[40] or "unreasonably dangerous."[41] Most drugs and vaccines can cause adverse reactions that the current state of science cannot prevent without nullifying the beneficial effect of the product.[42] Comment k of the Restatement recognizes this, in effect, by exempting "unavoidably unsafe products" from strict liability.[43]

In its 1985 decision in *Kearl v. Lederle Laboratories,* however, the California Court of Appeals criticized the "rather routine and mechanical fashion" in which courts have found that vaccines were unavoidably unsafe.[44] In particular, it rejected the contention that all vaccines are, by definition, "unavoidably unsafe products" that, if accompanied by proper direction and warning, are always exempt from strict liability. Rather, it suggested that vaccines may contain "defects that could have been avoided by better manufacturing or design."[45] The implication was, of course, that some vaccines carry risks that could have been detected and eliminated or protected against had the manufacturer undertaken appropriate investigation or changes in the configuration or the specifications of the vaccine itself.

The court suggested that each vaccine be evaluated to

determine whether it is unavoidably unsafe, on the basis of the following factors:

1) Whether, when distributed, the product was intended to confer an exceptionally important benefit that made its availability highly desirable;
2) Whether the then-existing risk posed by the product was both "substantial" and "avoidable"; and
3) Whether the interest in availability (again measured at the time of distribution) outweighed the interest in promoting enhanced accountability through strict-liability design-defect review.[46]

These factors are intended to provide a method of distinguishing between vaccines whose risks outweigh their benefits and those whose benefits outweigh their risks. The *Kearl* court concluded that the former should not be considered unavoidably unsafe products but should be subject to strict liability. A vaccine that meets all the above requirements should be exempt from design-defect strict liability. However, the court indicated that the manufacturer of such an unavoidably dangerous product could be challenged for negligence in design.[47] Under the negligence standard, a vaccine would be judged in light of the manufacturer's actual or constructive knowledge at the time of distribution, rather than by consumers' expectations or current scientific knowledge, as in true strict liability.

The result is an analytic schema for limiting liability to that for negligent design in cases involving unavoidably dangerous vaccines whose benefits make their availability highly desirable, as long as the need to distribute the vaccine is greater than the need to hold manufacturers accountable for injury. This schema provides criteria for determining the propriety of exempting individual vaccines from strict liability, in particular those grouped uncritically under the comment k rubric. To this extent, it represents a significant improvement over less rigorous analyses.[48] At the same time, it raises questions about the possibility, in practice, of determining when the risks of a vaccine have been adequately minimized. Vaccines that can be shown to have been developed without sufficient research and testing are theoretically subject to strict liability. How can a producer be sure that its research, development, and testing procedures will be considered adequate when adverse reactions materialize in the future?

As with other causes of liability, the perception of liability may be more influential than the reality. The application of strict liability to any vaccine remains theoretical to date. The *Kearl* court suggested that even under its own criteria, strict liability would not apply to the oral polio vaccine it reviewed.[49] While at least one court has adopted a similar rule, no reported decision has yet subjected any vaccine to this form of strict liability.[50] In fact, a recent decision of the Kansas Supreme Court stated flatly: "Public policy requires that the mere manufacture of the vaccine not be actionable on the ground of design defect."[51] This suggests that most courts are not prepared to make the distinctions proposed in *Kearl,* or may believe that the need for vaccines overwhelms all other considerations.[52]

Even using the *Kearl* criteria to identify unavoidably unsafe products, an AIDS vaccine should meet the three tests for exemption from strict liability. Almost any candidate vaccine would be a necessary and useful product that warrants prompt distribution today. If pharmaceuticals such as AZT or other forms of treatment should prove highly useful, however, the relative benefits of a vaccine may decline, and with it, the public policy reasons for exemption from strict liability. At the same time, the existence of an effective treatment may allow more time and freedom for testing candidate vaccines.

The second *Kearl* criterion, covering the nature of the risk posed by an AIDS vaccine, could produce varying results depending upon the candidate vaccine. A vaccine derived from live, attenuated HIV is already thought capable of inducing cancer, if not AIDS itself, constituting a "substantial" risk. A vaccinia-vector vaccine may pose the risk of vaccinia, especially in the growing population that has not been vaccinated against smallpox.[53] Genetically derived vaccines do not appear to have any such risk, although other adverse reactions, unrelated to AIDS, might occur. In any event, it appears that the research community is exploring the range of vaccine types with sufficient diligence to satisfy any requirement that a resulting vaccine pose the least risk of the feasible options.

The public interest in having an AIDS vaccine available promptly is likely to outweigh any interest in holding manufacturers accountable for injury by means of strict liability. The public interest clearly lies in encouraging the development of new vaccines. There is little to be said in favor of holding manufacturers liable for unknown and unknowable risks during the early years of testing and distribution. Strict liability seems more appropriate with respect to vaccines with significant risks that have been on the market for many years. In such cases, the goal of spreading the financial risk, if not of encouraging vaccine safety, may justify making the manufacturer responsible for adverse reactions. Indeed, comment k specifically mentions new or experimental drugs as prime examples of unavoidably unsafe products because of the limited amount of information about them, compared with products that have been in use for some time.[54]

If the manufacturer of a new AIDS vaccine would not be strictly liable for any injury caused by the vaccine, might it not be held accountable in negligence for defects in design? Unless research is conducted with a degree of indifference or disregard for the evolving science that has not characterized the study of HIV, it would be virtually impossible to substantiate a claim of negligence in the development of the new vaccine. The reasons for considering

a new vaccine an unavoidably unsafe product also argue against the likelihood of finding negligence in designing the vaccine. With respect to design defects, strict liability essentially uses a negligence standard. While a claim of negligence focuses on the conduct of the manufacturer and not, as in strict liability, on the danger posed by the product, the sufficiency of the product's design depends upon the manufacturer's action in developing and testing it. Moreover, the level of information for which a manufacturer is held responsible is lower in negligence than in strict liability. Traditionally, negligence is based on the knowledge available to the manufacturer at the time of marketing or distribution.[55]

One difficulty in applying this standard may arise from the secrecy with which some preliminary AIDS vaccine research is being conducted. Manufacturers are deemed to know whatever information is available in the scientific community. This means that they may not avoid liability by neglecting to keep up with the state of research. At the same time, it does not require them to know the unknowable. Thus the information for which they are likely to be held responsible should be limited to that available in the literature and presented at scientific meetings. Ironically, while such a standard may protect manufacturers, it does nothing to encourage the kind of information-sharing that theoretically characterizes the scientific method and that would undoubtedly advance the development of an effective vaccine itself.

Removing Barriers to Vaccine Development

FDA Commissioner Frank Young has said that "we are really at sea" in trying to anticipate the effects of liability law on the production of an AIDS vaccine.[56] If fear of liability inhibits producers from pursuing research or seeking to market a vaccine, the battle against AIDS will have lost a most valuable weapon. Therefore, it is critical to clear away any misperceptions that impede progress toward vaccine development and to remove any barriers that serve no real purpose. The task of halting the spread of AIDS is difficult enough without jousting at windmills.

Although cases like *Kearl* have generated fear of an increased probability of liability, most reported cases have found vaccines to be unavoidably unsafe products whose risks do not amount to a design defect for which the manufacturer can be held financially accountable. For those few cases in which the risks of a vaccine might be found to have been avoidable, the negligence standard is likely to require no more stringent a duty of care than is already imposed upon manufacturers. This is to say that even if the *Kearl* and *Toner* approaches to evaluating the avoidability of vaccine risks are accepted in other states, they are not likely to impose liability beyond that for negligence in research and testing. Thus fear of liability for design defects may simply be fear of any liability at all. But it would be hard to make an argument that manufacturers should not be held responsible for negligence in developing and testing a vaccine.[57]

A variation on this argument holds that compliance with FDA rules and regulations and, ultimately, FDA approval and licensing of a vaccine entail, by definition, a finding that the vaccine is not in any way defective in design, that there has been no negligence. Accepting this argument, however, would remove all vaccines (and drugs) from tort scrutiny. As a practical matter, of course, FDA licensing will provide persuasive, if not conclusive, evidence that no negligence was involved in the development of a vaccine. But it ought not dispose of the matter. The FDA, after all, reviews the vaccines brought to it by manufacturers; it does not generate its own developmental research to select among candidate vaccines. While the agency's experience and expertise enables it to rigorously evaluate the manufacturer's selection, it has no power to insist that a manufacturer pursue particular lines of research. It may be that imperfect as it is, liability law provides the only real incentive now existing for ensuring that the initial choices are as well informed as possible.

Regardless of the care with which an AIDS vaccine is designed, adverse reactions are inevitable. Thus it is also inevitable that manufacturers should seek to protect themselves from liability for resulting injuries by warning both physicians and consumers of the risks inherent in vaccination. Here again, manufacturers' complaints about their uncertainty as to whom they should warn and what the warning should say seem to reflect their desire not to be responsible for providing any warning to consumers at all. While it may be difficult to construct a method of disclosing risks that every prospective vaccine recipient could understand, the law does not require so much.[58] To avoid liability, a manufacturer need only prepare nontechnical warnings of all known risks, including notice that not all risks are yet known. The obligation to provide warnings buttresses the obligation to conduct responsible research and testing in order to identify possible risks within the capabilities of existing scientific knowledge.

The strong possibility that manufacturers can avoid liability by providing complete disclosure[59] leaves unresolved the other side of the problem of adverse reactions—the injured vaccine recipient. A consumer who voluntarily takes the vaccine after being adequately warned of the risks is responsible for the consequences of his or her decision, and forfeits any claim against the manufacturer. This result may be hard to accept when the victim has little real choice but to be vaccinated. The first group for whom public sympathy may arise is the human subjects in whom the vaccine is tested in clinical trials. If something goes wrong, are the injured to be left to manage on their own? If the test group consists of individuals at high risk of acquiring the HIV infection, as is probable, the majority may be young homosexual men or IV drug abusers who have lit-

tle, if any, health insurance and possibly inadequate assets to survive and manage on their own. Who should be responsible for their care?

Similar questions gave rise to the National Childhood Vaccine Injury (NCVI) Act of 1986, which authorized a federal compensation program for persons who suffered certain injuries following immunization with vaccines against seven infectious diseases of childhood.[60] The act recognizes a degree of social responsibility to assist persons who are seriously disabled as a result of vaccinations that are required for children to enter school or day care throughout the country. It does not, however, apply to injuries from vaccines that are not required by law or regulation. Thus even if the act is implemented in the future, it will offer no protection to persons who take the AIDS vaccine.

It would be difficult to expand the NCVI act, as currently written, to cover AIDS vaccines without including all vaccines, whether or not they are required by law. The fundamental purpose of the act is to compensate those few who, in helping to prevent the spread of disease by taking a mandatory vaccine, suffer the unpredictable adverse reactions, especially since they are unlikely to obtain compensation through the tort system. The inclusion of a new, elective vaccine would require acceptance of a much broader principle of social responsibility for any vaccine-related injury. There is also a practical obstacle to extending the NCVI act to cover AIDS vaccines. In order to simplify the process of determining eligibility for compensation, the act presumes that certain injuries have been caused by the vaccine. It will then be virtually impossible to identify the kinds of reactions that may occur and the times of onset in order to establish a credible schedule of compensable injuries before any AIDS vaccine is tested or distributed. Therefore, the NCVI act itself does not appear to offer a useful model for compensating those injured by a new AIDS vaccine.

Would it be preferable to establish a program specifically for AIDS vaccines? In the fall of 1986, California enacted legislation intended to encourage research and development of an AIDS vaccine and to compensate injured persons.[61] The legislation provides for a state subsidy to California companies for clinical trials and guarantees the purchase of up to 500,000 units of vaccine at no more than $20 per dose if fewer than 750,000 units of vaccine are sold. It also creates an AIDS Vaccine Victims Compensation Fund to assist persons who are injured as a result of vaccination with an AIDS vaccine that has been approved and licensed by the FDA and sold, distributed, administered, or dispensed in California. But the fund is not available for injuries from vaccinations performed in clinical trials, so that the most vulnerable population has no recourse but private insurance and tort actions.[62]

Like the federal NCVI act, the California law attempts to limit the liability of manufacturers for vaccine-related injuries. But while the federal act does so by effectively eliminating the manufacturer's duty to warn consumers directly of vaccine risks, California codified the *Kearl* criteria for determining whether a vaccine may be subject to design-defect strict liability. In order to minimize the possibility that an AIDS vaccine could be considered avoidably unsafe, the statute states that any FDA-approved AIDS vaccine sold in California "shall be conclusively presumed" to be "intended to confer an exceptionally important benefit on society that makes its availability highly desirable,"[63] thereby satisfying the first of the *Kearl* criteria.

While the California legislation is a creative attempt to reconcile the reluctance of manufacturers to proceed without some limitation on liability and the need to compensate victims of the inevitable injuries, it falls short of protecting either group completely. Part of this is attributable to the uncertainty surrounding possible reactions to a vaccine and the extreme difficulty of determining whether particular injuries are caused by the vaccine itself, especially in clinical trials.[64] But at bottom the issue is one of public policy. Special legislation for AIDS vaccines raises the question of whether adverse reactions to an AIDS vaccine ought to be treated differently from injuries due to other causes. Is it fair to limit the liability of those who produce AIDS vaccines when manufacturers of other products are not protected? Is it fair to help those injured by AIDS vaccines when those with the disease itself receive no special help?

The only certainty in the debate is that it will be impossible to ease the burden of *both* manufacturers and injured persons by altering the rules of tort law. Changes that limit liability reduce the number of persons who can obtain compensation, while changes that expand the bases for recovery increase liability costs and may threaten the availability of an AIDS vaccine. The task for public policy is to develop ways to ensure a safe and effective vaccine supply and at the same time provide for the care of those who are injured. Since these are two distinct goals, they need not necessarily be accomplished by the same means. This is to say that compensation need not be linked to responsibility for injury in all cases.[65]

Liability law has been forced to serve as a social insurance system largely because the persons injured have no assured way of covering their health care expenses and loss of income. It is not unreasonable to assume that a comprehensive system of public and private health insurance and disability income assistance would eliminate the need for most injured persons to seek compensation through the tort system. Liability law might continue to serve whatever deterrence function it can by applying to the most serious cases of disregard for safety. While the argument for such a system must be made elsewhere, this model supports

the idea that it is possible, in principle, to reconcile the conflicting needs of the many participants in vaccine research and disease control. The AIDS epidemic demands prompt and effective action. It is time, therefore, to consider options beyond simple limitations on liability.

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38. The number of vaccine producers has already declined significantly, partly because of fear of liability. Institute of Medicine, supra note 36; Mariner and Clark, supra note 36.

39. American Law Institute, supra note 32.

40. Comment g to sec. 402A defines "defective condition" as "a condition not contemplated by the ultimate consumer, which will be unreasonably dangerous to him."

41. Comment i to sec. 402A defines "unreasonably dangerous" as a danger "beyond that which would be contemplated by the ordinary consumer who purchases it, with the ordinary knowledge common to the community as to its characteristics."

42. Institute of Medicine, supra note 36.

43. Comment k provides, in part: "There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidable high degree of risk which they involve. Such a product properly prepared, and accompanied by proper directions and warning, is not defective, nor is it *unreasonably* dangerous."

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52. Brown v. Superior Court, 227 Cal. Rptr. 768, 774 (Cal. App. 1st Dist. 1986).

53. Redfield et al., supra note 22.

54. Comment k states that its limitation on liability "is also true in particular of many new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognizable risk."

55. Willig, supra note 48.

56. Remarks to the Harvard University Division on Health Policy Research and Education, Health Science Policy Working Group, Subgroup on Regulation, Boston, Massachusetts, March 31, 1987.

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60. The act was signed into law in November 1986 without an initial funding mechanism, so it remains to be seen whether and how it will be implemented. The act covers listed disabilities that are deemed to result from vaccination against diphtheria, pertussis (whooping cough), tetanus, polio, measles, mumps, and rubella, most of which are required for school entry in all the United States. Compensation is to be paid for medical expenses over $1,000, actual and anticipated losses of earnings, and up to $250,000 for non-economic injuries; $250,000 is payable in the event of death. Limitations on the kind and amount of compensation payable are imposed depending upon the date of the vaccination in question. Claims are to be submitted to a United States district court for determination. Claimants may accept the decision of the court or may file a civil action seeking damages if they have a cause of action.

61. California Health and Safety Code, chap. 1.14 (1986). California also has a limited program of compensation (up to $25,000 in medical expenses) for persons injured as a result of a vaccination required for children under California law. Calif. Health and Safety Code, §429.35. For a description of that program, see Mariner WK, California's compensation system, in Comparison of compensation programs for vaccine injury, report to the National Center for Health Services Research and Health Care Technology Assessment, 1986: 101–21. North Carolina enacted a compensation program in 1986 similar to the federal system, but it may lapse if the federal scheme is funded.

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