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ASSESSING COMMERCIAL FEASIBILITY: A PRACTICAL AND ETHICAL PREREQUISITE FOR HUMAN CLINICAL TESTING

DWAYNE D. KIRK

School of Life Sciences, Arizona State University, Tempe, AZ
The Biodesign Institute, Arizona State University, Tempe, AZ

JASON SCOTT ROBERT

Center for Biology and Society, Arizona State University, Tempe, AZ
School of Life Sciences, Arizona State University, Tempe, AZ

This article proposes that an assessment of commercial feasibility should be integrated as a prerequisite for human clinical testing to improve the quality and relevance of materials being investigated, as an ethical aspect for human subject protection, and as a means of improving accountability where clinical development is funded on promises of successful translational research. A commercial feasibility analysis is not currently required to justify human clinical testing, but is assumed to have been conducted by industry participants, and use of public funds for clinical trials should be defensible in the same manner. Plant-made vaccines (PMVs) are offered in this discussion as a model for evaluating the relevance of commercial feasibility before human clinical testing. PMVs have been proposed as a potential solution for global health, based on a vision of immunizing the world against many infectious diseases. Such a vision depends on translating current knowledge in plant science and immunology into a potent vaccine that can be readily manufactured and distributed to those in need. But new biologics such as PMVs may fail to be manufactured due to financial or logistical reasons—particularly for orphan diseases without sufficient revenue incentive for industry investment—regardless of the effectiveness which might be demonstrated in human clinical testing. Moreover, all potential instruments of global health depend on translational agents well beyond the lab in order to reach those in need. A model comprising five criteria for commercial feasibility is suggested for inclusion by regulators and ethics review boards as part of the review process prior to approval of human clinical testing. Use of this model may help to facilitate safe and appropriate translational research and bring more immediate benefits to those in need.

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Address correspondence to Dwayne D. Kirk, School of Life Sciences, Arizona State University, P.O. Box 874501, Tempe, AZ, 85287-4501, USA. E-mail: dwayne.kirk@asu.edu

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Introduction

Usually when commercial issues enter into debates about research integrity, the issues are personal and institutional conflicts of interest, suppression of negative findings, or the social and ethical sequelae of science (and bioethics) "in the private interest" (Krimsky, 2003; see also Lewis et al., 2001; Gibson et al., 2002; Resnik and Shamoo, 2002; Sugarman and McKenna, 2003; Elliott, 2005). These are all important concerns. Our focus is somewhat different. Proposals for research funding and protocols submitted for ethics review often include dramatic promises of the likely impact of the research, typically as part of "knowledge translation." The peer-review process for competitive research funding considers, *inter alia*, the novelty of the proposal, the validity of the underlying science, and the probability of achieving its aims. When the funding is meant to support human clinical testing, and certainly when an Institutional Review Board (IRB) reviews a protocol, we propose that the latter criterion is especially important, and moreover, that the treatment or product being evaluated must have some reasonable chance of being provided to the target population. We contend that in addition to reasons of standard safety or efficacy failures, or even product affordability, access to experimental drugs and vaccines may often be negated as a result of limitations on commercialization (especially product design, development, and manufacturing). Further, we contend that, although commercial enterprises have typically conducted a business case analysis prior to embarking on human clinical testing, this underlying premise for new product development is rarely considered by academic researchers. We propose that in order to maximize the value of human clinical experiments—a core component of ethical human subjects research—an assessment of commercial viability should occur prior to experimentation on human subjects, and would be beneficial even earlier in the process of research design.

Our perspective is grounded in two related concerns. First, without a deliberate assessment of commercial feasibility—particularly for new platform technologies—the nature of the clinical materials and the trial design itself may not be aligned with the true developmental priorities for that technology. This reduces the value proposition in return for human volunteers in research, and may necessitate duplication of clinical trials for the sake of minor improvements in product or process aspects. A lack of regard for the potential economic factors required for complete product development and manufacturing might result in wasted resources, including public funding and clinical research facilities. Secondly, in the case of early-stage therapeutics and devices, the temptation for academic researchers to quickly generate primary data (for purposes of publication, patenting, or competitive funding opportunities) may often override rational development, optimization, and validation of the technology prior to human clinical testing. This again may result in testing an inferior product or result in exposure by human volunteers to unnecessary risks in the form of immature products. In the case of novel therapeutics, the demand for translation of clinical research into health practice is so complex as to possibly undermine the initial justification for the clinical studies in the first place. This is particularly evident in the call for new vaccines and drugs for application in developing countries where improved global health is leveraged as a major promise within the research proposal. Merging these concerns, we conclude that commercial feasibility might be an important tool in focusing and accelerating clinical development, while also protecting the rights of human subjects. Without an adequate assessment of commercial feasibility, the exposure of human volunteers may have less than optimal value, and proceeding with unknown risks in unproven systems that may never reach the intended market—even if they work—poses significant ethical concerns.

Plant-made vaccines (PMVs) in particular have been offered as a global health solution for reducing the burden of infectious disease in developing countries, and we offer this technology as a model system for exploring this new perspective for assessing the value of and ethical considerations in human

clinical testing and its funding. We begin by reviewing the science of plant-made vaccines and some of the promises made on its behalf. We then argue that assessments of commercial feasibility would likely have improved the technical and ethical components of clinical testing with PMVs (and other products), and conclude with a model for the determination of commercial feasibility for regulatory use.

Promising Global Health Through PMVs

In the developed world, at least thirty-five vaccines are licensed for immunization against infectious diseases such as polio, measles, mumps, hepatitis B, and pertussis. Such once-deadly diseases now pose little threat to our health and the health of our children. Yet more globally, cost and distribution difficulties of required vaccines remain a major hurdle in developing countries. Infectious diseases still account for approximately 30% of all deaths and for as many as 63% of children's deaths worldwide (Ratzan et al., 2000). In low income regions such as Africa, infectious diseases account for up to 49% of all deaths compared to just 2% in Europe (Ratzan et al., 2000). This is largely the result of a combination of economic organization, low standards of hygiene, and high risk of exposure. The most prominent diseases in developing countries are respiratory infections, AIDS, tuberculosis, malaria, and diarrheal diseases, which include disease agents such as Rotavirus, cholera, Enterotoxigenic *Escherichia coli*, and noroviruses. These agents and tropical diseases such as dengue fever and malaria remain in desperate need of a good vaccine but are technically difficult targets for existing technologies.

Due to a range of advantages in protein production and product storage, scientists are now actively pursuing vaccine production in alternative systems such as transgenic plants or plant cells, virus-mediated expression in plants or insect cell cultures, and transgenic animals (reviewed by Twyman et al., 2005). Plant-made vaccines are created by genetically engineering plants, plant cells, or plant viruses (which are subsequently used to infect plants) to produce vaccines, based on individual protein antigens which are capable of generating an appropriate

immune response to protect against disease. The plant tissues are harvested and either processed by methods such as milling or freeze-drying for oral delivery, or purified for delivery by injection, intranasal or topical application. The claimed advantages of PMVs over conventional vaccines have been reviewed by Kirk and Webb (2005). The potential environmental and health risks associated with PMV production have been described in detail by Kirk et al. (2005), and the ethical dimensions of PMV research and development have been surveyed by Robert and Kirk (in press).

Once a PMV makes it to a Phase I clinical trial, a wide range of ethical considerations arise, including issues of fair subject selection, informed consent, the geographical location of clinical trials (the local regulatory framework and demographics of the subject population), and appropriate independent review of the proposed studies (Emanuel et al., 2000; see also Levine, 1988; Sugarman, 1999; Robert and Kirk, in press). It is inevitable that there will be unknown risks in any clinical research involving human subjects who receive an experimental drug, device, or treatment. The greatest concerns for patient welfare with delivery of PMVs is that they may either cause oral tolerance (loss of immune sensitivity and ability to mount response to the authentic disease), or allergenicity to the vaccine, or to other dietary proteins when adjuvants are used to broadly increase the immune responses to materials delivered orally (see Kirk et al., 2005). While both of these effects are hypothetical and improbable with just 2–3 doses of an oral vaccine, such a negative reaction could be significant in altering the general health and dietary tolerability of a volunteer. Moreover, the risk of ingesting genetically modified (GM) plant materials is unknown and very difficult to quantify. In consideration of these potential risks, the ethical characteristics of testing PMVs in humans are quite different from clinical testing of conventional vaccines, but are nonetheless familiar issues in human subjects research.

Beyond these issues of trial design and execution, there are additional ethical concerns that must, we maintain, be addressed at the clinical trial stage. To date, these ‘upstream’ concerns have received less attention in the ethics literature. The focus of this discussion is the desirability of adequately

demonstrating the commercial feasibility of drugs, devices, or other therapeutics—that is, the likelihood that they will ever be produced in such a way as to be broadly available to relevant publics. While such a consideration may not always be appropriate, in the case of plant-made vaccines it is of central concern, inasmuch as the most common public justification for developing this alternative to conventional vaccines is to benefit those in developing countries for whom access to conventional vaccines cannot be secured for financial or logistical reasons. Indeed, a common justification of PMV research for human use is to improve global health by immunizing the developing world at "just pennies a dose."[1] PMVs are thus widely seen as an appropriate response to the persistence of infectious diseases that are otherwise neglected in the developing world.

But what is the evidence that innovation in plant-made vaccines will lead to improvements in global health? How, if at all, will the technical innovation be translated into improved health outcomes? The problem of global health is immense, and the use of plants as a vaccine production system is a novel approach to this problem. But there has been a lack of demonstration of how this technology will be developed and reliably manufactured to meet the needs of developing countries. If a business case cannot be developed to demonstrate manufacturing PMVs with sufficiently low cost of goods for use in the developing world, or with sufficient market demand for private investment, is it ethical to proceed with publicly funded clinical trials of plant-made vaccines which are proposed specifically for developed nations? We do not wish to indicate that public funds should not be used to develop solutions to issues of global health, or that all publicly funded research must have a translational aim; rather, where translation is promised in exchange for public funds, funds should be disbursed with reasonable confidence that a realistic pathway for product development, testing, approval, and product manufacturing will emerge.

[1]See http://www.gene.ch/genet/2005/May/msg00042.html and http://www.forbes.com/technology/free_forbes/2003/0120/110.html (last accessed August 8, 2005).

Commercial Feasibility as a Predictor of Knowledge Translation

While researchers (predominantly in the academic sector) continue to work on issues of technical feasibility, immunizing the developing world at just pennies a dose, or at all, will depend very heavily on a range of factors that are largely independent of the technology itself. A technically feasible PMV technology may not be either politically or economically feasible. By analogy, consider that there is enough food surplus in the West to feed the least well off in the developing world, and yet we are unable to effectively distribute that surplus, largely because of logistical and financial hurdles. PMVs might achieve the goal of improving global health only if they can be manufactured and distributed in line with technical, economic, and political feasibility. While political factors may remain unpredictable and difficult to control, and while economic forecasting is itself rife with challenges, scientists can and should engage in commercial feasibility analysis of PMV research, which should help to mitigate both technical and economic considerations, and so facilitate knowledge translation.

Negotiating the product development process beyond technical innovation takes considerable financial resources, with the end goal of translating research and development into a safe, consistent, and potent pharmaceutical. Admittedly, knowledge translation (KT) is no easy feat and is not restricted to the problems of global health. In biomedical research, KT may be measured quantitatively in terms of patenting or licensure and/or uptake into clinical or public health practice. Contopoulos-Ioannidis et al. (2003) studied articles published in six top basic science journals (*Cell*, *Journal of Biological Chemistry*, *Journal of Experimental Medicine*, *Nature*, and *Science*) between 1979 and 1983; their inclusion criterion was articles that specifically promised significant clinical applications. Allowing a full two decades for the promised clinical applications to mature and manifest in practice, Contopoulos-Ioannidis et al. (2003) determined that of promises made in 101 articles, only 27 technologies proceeded to clinical trials, of which only 19 generated positive results published in the literature. Of the basic science innovations reported in those journals between 1979 and 1983, only 5 were in licensed clinical use in 2003, and only 1 had impacted current medical practice.

The greatest predictor of eventual clinical trials was some form of industry involvement in the initial publication.

Obviously, predictions are not always accurate, and we should not assume that the null hypothesis would be that all the promises made in those journal articles would have panned out. There are many sorts of confounders and obstacles to the translation of basic research into clinical practice, including product quality criteria, the use of oversimplified disease models in preclinical research, inappropriate research methods, conflicts of interest, and investigator bias (Ioannidis, 2004). While industry involvement in a publication (whether an industry author or industry-supported research) tracks well with the move from the bench to the clinical trial, it is also evident that industry skims the cream off the milk. Moreover, industry involvement also may bias research programs through the adoption of a profit motive and "orphaning" entire areas of inquiry, and by introducing and reinforcing conflicts of interest (for discussion see Sugarman and McKenna, 2003).

At present, the absence of sufficient revenue incentive for development of PMVs for orphan diseases (diseases of lower income populations, largely neglected or abandoned by vaccine developers) by industry presents a particularly dismal outlook for translation of this technology into global health solutions, both as a platform in the first instance and subsequently for individual products. PMVs might not be able to be manufactured with sufficiently low cost of goods to address affordability issues in developing countries (Kirk and Webb, 2005). Maturation of the PMV technology (indicated by product licensure) might not occur unless major corporate or philanthropic investment is first provided to develop a vaccine with sufficient importance and market demand in developed countries, and thereby drive maturation of the technology (Robert and Kirk, in press). These arguments run counter to the promises made by academic researchers that PMVs will be cheaper than other production systems and manufactured as a priority for developing countries. Nonetheless, significant investment from corporate or philanthropic sources will be necessary for development of PMVs, including the tremendous costs of clinical testing and manufacturing, before the technology is capable of addressing orphan infectious diseases.

To date, six human clinical trials have been conducted with PMVs, generally with very crude preparations, to assess basic indicators of safety and efficacy in humans (Tacket et al., 1998; Kapusta et al., 1999; Tacket et al., 2000; Thanavala et al., 2005; Yusibov et al., 2002; Tacket et al., 2004). Robert and Kirk (in press) provided a timeline of the developmental activities in the PMV field, with a summary of the clinical trial designs and results to date. Kirk and Webb (2005) stressed the need to consider the complete path for product development before contemplating further Phase I clinical testing with crude materials. More complete preclinical testing (including formal toxicity testing of final formulations) and Phase I clinical testing is likely to be required, including dose escalation trials, and optimization of dose presentation and timing schedules. Progression of experimental materials to Phase II and III clinical trials requires a validated manufacturing process, consistent methods for accurately assessing product quality, a viable product definition, and accepted standards for gauging efficacy in the target population. No PMVs have yet progressed to Phase II clinical testing, and many of these product elements are missing from current academic projects in this field despite 15 years of research and development with public funding.

Figure 1 provides a simplified linear model for new pharmaceutical development (for a more detailed development plan for PMVs see Kirk and Webb, 2005). The PMV technology is still in the early stages of this technology lifecycle, with continued focus on introducing the technology and establishing a path for product development. Despite the many researchers in this field (for a full review see Twyman et al., 2005), a dominant design has yet to emerge and the current focus is limited to Research and Development (R&D) and preclinical activities, with some necessary overlap into Early Clinical Testing and Regulatory aspects. Attempting to achieve complete vertical integration to satisfy all of the necessary steps for product development would require

FIGURE 1 A simplified linear model for product development in the pharmaceutical industry.

tremendous capital investment. Even if a promising PMV candidate emerged from early clinical testing with very positive results, development costs for formulation and dosing studies, manufacturing, and late-stage clinical testing could easily range from $100M to $500M for a single product—an investment that would appear to be beyond practical levels for most philanthropic sources, particularly for the sake of enteric diseases or replacement vaccines (the majority of current PMV projects), and which might be better applied towards global health in other areas—such as purchasing existing vaccines or investment in solving problems of hygiene, water quality, or sustainable agriculture.

But perhaps complete vertical integration is not required. The model for determining commercial feasibility that we present here should allow for feedback and feedforward loops to yield more rational research and product development. In the context of explicitly translational research, downstream considerations, insofar as they are predictable early on, should feed into upstream R&D and preclinical testing (see Figure 2). This more dynamic approach to research and product development will yield two important benefits. First, we should be able to identify early in the product development process where targeted infusion of funding will be required to facilitate manufacturing and distribution; secondly, we should be able to minimize risks to human volunteers by restricting human clinical testing to genuinely feasible products. These aims are facilitated by embedding an assessment of societal outcomes into the research and development process (as more formally proposed by Guston and Sarewitz, 2002).

We do not wish to suggest that development of PMVs should be arrested because of poor potential for KT, but rather that academic and clinical researchers should be at least reasonably sensitized to the many challenges for product success as a larger

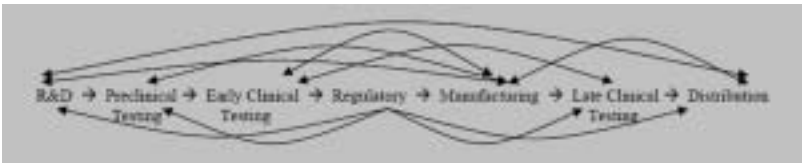

FIGURE 2 A simplified dynamic model for product development in the pharmaceutical industry.

picture, should focus their investigations to address the major manufacturing weaknesses earlier rather than later, and should consider whether other aspects of product or process improvement are more critical to success than clinical testing at a particular point in time. Our worry is that plant-made vaccine scientists are setting themselves up for KT failure—and broken promises to improve global health—by insufficiently attending to all manner of variables beyond proof-of-concept and preclinical testing with crude formulations.

While academic scientists may not, at present, have the necessary skills to conduct commercial feasibility analyses on their own, they should be encouraged to collaborate from the outset with those who do—such as project managers, business planners, and researchers engaged in technology assessment. A business case analysis would at least contribute to the rigorousness of the clinical development strategy by forcing practical issues of manufacturing, product quality, and market economics to be addressed at the product concept stage, and not further downstream after human subjects testing is completed (and possibly made irrelevant by changes in product strategy). A preclinical requirement to engage in commercial feasibility assessment would, we believe, have crystallized many of the weaknesses that appeared in early PMV clinical materials, such as up to 4-fold variability in antigen dose delivered by consumption of large volumes of perishable materials (see Robert and Kirk, in press). This would likely have accelerated the development of more appropriate preclinical materials, and allowed for greater accountability on the part of PMV researchers.

A Model for Future Regulation of PMV Research

Currently, there is no specific section in an Investigational New Drug (IND) application to the Food and Drug Administration (FDA) which requires either a justification for why human testing is the best or only alternative at this time, or any description of the likelihood or intended path to commercialization. We assume that the absence of these elements from the formal regulatory process for Phase I trials is due to an inherent assumption that private companies would not be entering into clinical testing without having already conducted their own manufacturing and

market analyses. When vaccine research and development are undertaken within explicitly corporate contexts, commercial feasibility must be demonstrated as part of the business analysis. However, the ability to obtain public funds to conduct these trials obviates the need for equivalent forethought by academic researchers, and opens the possibility of human testing without any underlying commercial feasibility. When the R&D takes place in a more academic setting—even when the aim is commercial licensure—the demonstration of commercial feasibility has to date not been required, and plant-made vaccines are a case in point. With the rapid increase in funding for academic institutions to develop biotechnology applications, a larger number of clinical trials are likely to be conducted without this commercial analysis.

We suggest that it is reasonable for inclusion of such justification within the existing IND structure prior to clinical trials. The content of IND applications in the U.S. is specified under 21CFR312.23, and provides no section for defining product demand, commercial feasibility, or for listing possible limitations which might prevent an experimental product from advancing to later stage trials—this is in direct conflict with the kind of consideration that we suggest should be diligently attempted by investigators before experimentation in humans. We suggest that such justification should also be required by Institutional Review Boards (IRBs) prior to approval of human trials. Corporate sponsors of clinical trials should already be in the position to provide this information, and the efficient use of public funds for clinical testing should be defensible in the same manner. The risks imposed upon trial volunteers may be unacceptable if the regulatory or economic drivers will not ultimately support commercialization (and hence distribution) of the product being tested. The additional benefit of applying this ethics consideration is a matter of public accountability, namely that human clinical trials will be more purposeful in design to achieve product development goals, and will utilize the best possible materials (more closely aligned with commercial product concepts) in return for public funds and exposure by human volunteers.

Prior to exposing human subjects to experimental pharmaceuticals such as PMVs, scientists should be required to make a *bona fide* effort to justify the commercial feasibility of the vaccine, particularly if public funds are utilized. As noted above, commercial

feasibility is a complex subject and is additional to technical feasibility. Technical feasibility for PMVs comprises aspects of gene expression, authenticity and stability of the antigen, and the ability for the plant formulation to stimulate the mucosal immune system for appropriate and consistent antibody or cell-mediated defense against infection. These aspects are critical to product success, but should be considered in parallel to establishing commercial feasibility. Technical feasibility is an obvious dimension of an ethical clinical trial, as a matter of scientific validity. We propose that in addition to these items, commercial feasibility should be considered in each case to judge the overall value and risk of human clinical testing with PMVs. The prerequisites for commercial feasibility are diverse. Table 1 provides a model for the assessment of commercial feasibility which could be applied to the ethical justification of clinical trial applications of plant-made vaccines.

By addressing each of the dimensions described, regulators may determine whether the risks to be borne by volunteers are warranted in return for likely benefits, including benefits to society—which is, of course, a notoriously difficult process (Weijer and Miller, 2004). But the use of these criteria by regulators would in turn force researchers to think more critically about the final form of the product, and thereby derive more advanced prototype materials before exposure to human volunteers. Until the items described in Table 1 can be assembled into a coherent pathway for commercial development of particular products, clinical testing with human volunteers will have indeterminate value. Clinical trial results may become redundant if trials need to be duplicated each time basic elements or production processes are altered.

Our proposal may have the effect of further slowing down the drug and device approval process. The FDA and IRBs will now demand, and be required to have the capacity to assess, commercial feasibility claims about products proposed for clinical research. That is a tall order. But refusing it may be ethically unacceptable. Well-designed, well-justified studies of good products with important potential benefits and demonstrable feasibility will not be affected as a result of our proposal. Other studies may indeed be delayed before entering clinical testing—and well they should.

TABLE 1 A model for early assessment of commercial feasibility, applied to plant-made vaccines

Dimension	Justification
Safety and efficacy	These elements are generally contained in the Pharmacology and Toxicology sections of the existing Investigational New Drug format, as a necessary tool of risk management prior to exposure to human volunteers.
Estimated market demand and distribution	Identify the global market, developing country demand or probability for adoption by agencies as a replacement vaccine. The value of testing vaccines with low probability of industry support should be compared to the associated risks for human volunteers and prioritized against high-demand vaccines. In conjunction with manufacturing and cost estimates, an estimate of financial investments and returns should be formulated – including a projected cost of goods using a justified cost model.
Manufacturing strategy and anticipated cost	Many plant systems have been reported but manufacturing models have not been validated. Early clinical testing using raw food materials could have been greatly improved if emphasis on consistent and processed materials had been applied during the IND process. The negative image of production through local food providers could have been invalidated much earlier, and regulatory agencies could provide early input to define acceptable manufacturing processes. A complete strategy should include definition of dose and product quality criteria.
Value of the proposed trial	A statement addressing how the data obtained from this trial will provide appropriate translational value in return for the opportunity for experimentation with human volunteers. This aspect should be weighed against opportunities for further preclinical or process development activities prior to clinical testing.
Freedom to operate strategy	A complex intellectual property environment may need to be scaled before contemplating public use of a potential new product. Academic researchers may not consider the network of third party agreements that could be necessary for product manufacturing; commercial developers are assumed to have done this analysis and initiated a licensing strategy as appropriate to achieve freedom to commercialize an effective product.

Conclusion

Our analysis of commercial feasibility assessment as a requirement of ethical research and KT yields three critical lessons: commercial feasibility assessment is (1) a significant component of the protection of human subjects from unjustified research risks, (2) an indispensable tool for researchers hoping to translate their technical innovations into real-world benefits, and (3) an important prerequisite for responsible, accountable research when KT is the underlying promise. With regard to (2), we expect that commercial feasibility assessment will assist with the design of research and the determination of critical elements in the pathway from innovation to application. With regard to (3), note that we are restricting our attention to research that has an explicit KT dimension, and not advocating that all research must be translational or commercially viable. And, finally, regarding (1), our argument is that clinical testing of new drugs such as PMVs should not receive financial support or IRB approval without adequate consideration of their ultimate commercial feasibility, the likelihood that they will ever reach their intended targets as a function of product design or manufacture. The five criteria described in Table 1 are suggested as a framework to allow consideration of commercial feasibility by IRB and FDA reviewers before human volunteers are exposed to an experimental vaccine.

While our argument has focused on PMVs as a model, we do not wish to suggest that PMVs should be held to standards higher than other pharmaceuticals. Plant-made vaccines are a convenient example, but they are not a unique instance. The situation we have in mind arises whenever research funds are sought to achieve some translational goal, and is compounded when the achievement of that translational goal is contingent on economic factors beyond the funded research, and when the research in question involves human volunteers and public funds. Under those conditions, we advocate the model proposed here.

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