

Private investment in AIDS vaccine development: obstacles and solutions

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Abstract The development of vaccines for the prevention of AIDS, malaria, tuberculosis, and other diseases requires both public and private investment. Private investment, however, has been far lower than might have been hoped, given the massive human toll of these diseases, particularly in the poorest countries. With a view to understanding this situation and exploring potential solutions, the World Bank AIDS Vaccine Task Force commissioned a study on the perspectives of the biotechnology, vaccine, and pharmaceutical industries regarding investment in research and development work on an AIDS vaccine. It was found that different obstacles to the development of an AIDS vaccine arose during the product development cycle. During the earlier phases, before obtaining proof of product, the principal barriers were scientific. The lack of consensus on which approach was likely to be effective increased uncertainty and the risks associated with investing in expensive clinical trials. The later phases, which involved adapting, testing, and scaling up production for different populations, were most influenced by market considerations. In order to raise the levels of private research and development in an AIDS vaccine there will probably have to be a combination of push strategies, which reduce the cost and scientific risk of investment, and pull strategies, which guarantee a market.

Keywords AIDS vaccines/economics; Investments; Financial support; Motivation; Cost-benefit analysis; Research; Drug industry; Private sector (*source: MeSH*).

Mots clés Vaccin anti-SIDA/économie; Investissement; Aide financière; Motivation; Analyse coût-bénéfice; Recherche; Industrie pharmaceutique; Secteur privé; Pays en développement (*source: INSERM*).

Palabras clave Vacunas contra SIDA/economía; Inversiones; Apoyo financiero; Motivación; Análisis de costo-beneficio; Investigación; Industria farmacéutica; Sector privado; Países en desarrollo (*fuentes: BIREME*).

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Voir page 726 le résumé en français. En la página 726 figura un resumen en español.

Background

Global investment in the development of preventive AIDS vaccines has been quite limited (1, 2). In 1999 only US\$ 350 million were spent by the public and private sectors on such work, nearly two-thirds of this amount having been disbursed by the National Institutes of Health in the United States of America (2). More than 25 AIDS candidate vaccines have been tested for safety and immune response in small groups of human volunteers but only one is being tested for efficacy in a large human population (2). Successful vaccine development requires both public and private finance, the latter making it possible to transform the science into a product that can be manufactured and

sold on a large scale. Why, in the face of the enormous impact of HIV/AIDS, is industry not investing more in vaccines? What obstacles limit further investment? How can private investment in research and development on AIDS vaccines be stimulated?

In the autumn of 1998 the World Bank AIDS Vaccine Task Force commissioned a study on the perspectives of the biotechnology, vaccine, and pharmaceutical industries regarding the barriers to greater investment in research and development on AIDS vaccines that would be effective and affordable in developing countries (3). The results were used to develop a framework for understanding industry's decisions on investment in vaccine development. Based on this framework a menu of mechanisms was identified which might influence private investment (4, 5). The present paper summarizes the main findings, the framework, and the views expressed about various mechanisms that might stimulate investment.

Study of industry perspectives

Representatives of a cross-section of private firms were selected to represent varying levels of commit-

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ment to the development of an AIDS vaccine (Fig. 1). Of the 20 European and United States companies contacted, 16 agreed to participate. Seven leaders from the AIDS vaccine research community were also interviewed (Box 1). The study collected information from each firm on current activities in AIDS vaccine development; perceptions of the potential market for AIDS vaccines, particularly in developing countries; barriers to AIDS vaccine development; and the probable extent to which various mechanisms would stimulate private investment (3).

Principal findings

Investment in research and development

Except in a few small biotechnology companies, the development of an AIDS vaccine was not the primary focus of vaccine development efforts (Fig. 1), but was only one component of a diverse portfolio. In 1998, fewer than 200 scientists in the private sector were dedicated to work related to AIDS vaccines, and some of them were probably supported by grants from the public sector. The private funds dedicated annually to research and development on AIDS

vaccines were estimated to be between US\$ 50 and US\$ 124 million.

Potential market for AIDS vaccine

Views on the potential market for an AIDS vaccine were diverse and predictive of the level of investment. The companies devoting the most resources to the development of such a vaccine believed that there would be a substantial market in industrialized countries. They also considered that the development path would be similar to that of the hepatitis B vaccine, i.e. rapid uptake in industrialized countries but slow uptake in developing countries. However, other firms held that any market in industrialized countries would be small and slow to develop, and some also believed that the probability of an AIDS vaccine ever being widely recommended in industrialized countries was small. These firms were less likely to be investing their resources in vaccine development.

Views on the potential market in developing countries were divided. Smaller biotechnology companies with limited or no experience in supplying vaccines assumed that there would be substantial

Fig. 1. Overall level of corporate AIDS vaccine research effort, 1998^a

	Sole activity	Major activity	Component of research/ drug portfolio	Minor activity	No evidence of current effort
	Importance for company				
Serious (evidence of sustained commitment over time)	VaxGen	Apollon Immuno AG Pasteur-Mérieux Connaught^b	Cel-Sci Chiron Glaxo Wellcome^c Merck	Genetech	
Moderate	Immune Response Corp. MicroGeneSys	Acrogen Agouron Pharmaceuticals Auragen/Agracetus AVR Corp. Cell GeneSys Gilead Sciences Immuno Science Inc. Vertex Pharmaceuticals Virus Research Institute	Abbott Laboratories Boehringer Ingelheim Bristol-Myers Squibb British Biotech DuPont Pharmaceuticals Hoffmann-LaRoche Immunex Corp. Therion Biologics Wyeth Lederle		Bayer AG Hoechst AG
Sporadic (one or occasional mentions)		IDT Inc. US Bioscience	Immusol Inc. MedImmune Inc. Progenics Pharmaceuticals Sequus Pharmaceuticals Shaman Pharmaceuticals Theratechnologies Inc. United Biomedical	Pharmacia & Upjohn SmithKline Beecham^c Steroidogenesis Inhibitors International Vical	

Source: A. Batson & P. Whitehead, 1998.

^a Companies in bold were interviewed.

^b Now Aventis Pasteur.

^c Now GlaxoSmithKline.

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Box 1. Experts interviewed by World Bank AIDS Vaccine Task Force, 1998

Barry Bloom (Harvard School of Public Health, Boston, MA, USA)
 Seth Berkley (International AIDS Vaccine Initiative, New York, NY, USA)
 John Moore (Aaron Diamond AIDS Research Center, New York, NY, USA)
 Anthony Fauci (National Institutes of Health, Bethesda, MD, USA)
 John La Montagne (National Institutes of Health, Bethesda, MD, USA)
 Jonathan Cohen (*Science* magazine, San Francisco, CA, USA)
 Richard van de Broek (Hambrecht & Quist, New York, NY, USA)

markets in developing countries and that sales would be adequate if an effective AIDS vaccine were developed. In contrast, the larger companies already supplying vaccines for the global market attached little or no commercial value to markets in developing countries, citing the slow uptake and lack of funding for such cost-effective products as hepatitis B and *Haemophilus influenzae* type B vaccines.

Barriers to increased investment

All companies cited important scientific uncertainties causing the development of an AIDS vaccine to be risky and expensive. Because AIDS is fatal and incurable, two of the commonest approaches adopted in the field of human vaccines, namely the use of live attenuated strains of the virus and inactivated whole virus, were considered inappropriate. Most efforts focused on approaches for which there were few or no current vaccine analogues. The scientific uncertainty was compounded by a limited understanding of the virus, a lack of correlates of immunity, and a lack of relevant animal models. Furthermore, it was not known whether a vaccine giving protection against one clade of HIV could be effective against others.

This uncertainty could be resolved most quickly by testing candidate vaccines in large-scale trials. However, testing the efficacy of candidate vaccines in large populations, i.e. in Phase III trials, involved major investment, US\$ 30 million per trial being a frequently quoted figure. Such trials were normally financed only after preliminary evidence had been obtained that the products were likely to be efficacious. In the case of an AIDS vaccine it was difficult to predict which approach would provide immunity. The result was a vicious circle in which the failure to undertake phase III trials perpetuated the lack of scientific knowledge that underlay industry's reluctance to invest their resources (Fig. 2).

Another barrier to investment concerned the need to invest in production capacity at an early stage. To make a product available shortly after licensure, investment in capacity had to be made early, before the results of an efficacy trial were known. The cost of production capacity for an AIDS vaccine intended to

be marketed in industrialized countries might be of the order of tens of millions of US dollars; in order to meet global needs the cost would be substantially higher. All or most of this investment would be lost if a viable commercial product did not result from the efficacy trials.

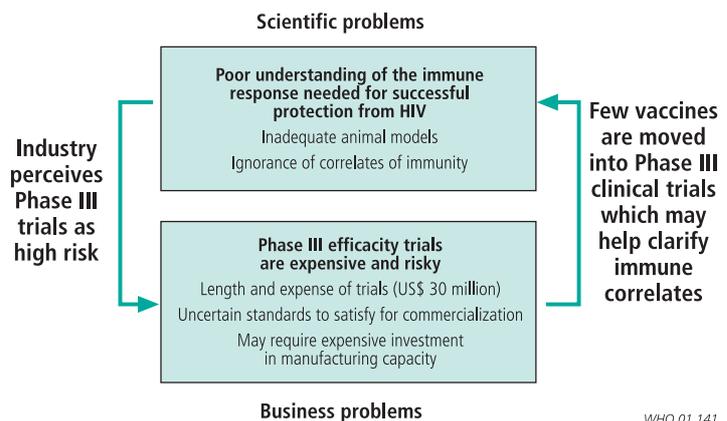
The uncertainty surrounding the science and future markets for an AIDS vaccine made it difficult to raise private funds for vaccine development. Nearly all the smaller biotechnology companies reported difficulties in raising capital. Most either limited their efforts on AIDS vaccines to work funded by public grants or relied on other activities to attract investment and pursued investigations on AIDS vaccines as part of a larger research platform. The difficulties faced by small biotechnology firms reflected the lack of confidence of the larger pharmaceutical companies that were typically a major source of investment and acted as a signal to the venture capital markets.

Stages of vaccine development

From the perspective of industry, product development involved a series of investment decisions corresponding to four distinct stages: 1. basic preclinical research; 2. identifying a candidate vaccine through non-human primate studies and tests of safety and immune response in humans; 3. developing and testing a candidate for a single market; 4. scaling up manufacturing capacity for that market. Fig. 3 illustrates the indicative costs and time needed to move through these stages. The low expectation of success, the high costs of trials, and concerns about negative publicity in the event of failure to deliver an efficacious product were important issues influencing decisions on investing in large-scale efficacy trials (stage 3) and increased production capacity (stage 4).

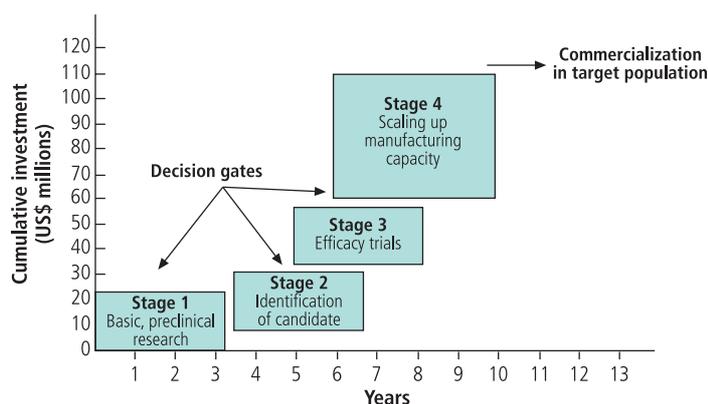
For a vaccine to be rapidly available for global use, investment would be necessary in adapting and testing it to ensure relevance (i.e. safety and efficacy in additional populations) and access (i.e. adequate manufacturing capacity and funding/pricing structures for the needs of developing countries). In order

Fig. 2. The vicious circle: scientific barriers make industry reluctant to invest in the Phase III trials that may be required to solve them



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Fig. 3. Stages and decision gates in AIDS vaccine development for a single population: industry's perspective^a



Source: A. Batson & P. Whitehead, 1998.

^a Estimated additional time and investment required for adapting and testing the vaccine for populations in developing countries: 6 years and US\$ 100 million, respectively.

WHO 01.142

to make a new AIDS vaccine broadly available at the earliest possible technical and regulatory opportunity, a manufacturer would have to make development and capital investments explicitly to support it for markets in the developing world. It was estimated that the incremental investment in capacity required to meet developing-country demand for a vaccine, i.e. hundreds of millions of doses, would be well over US\$ 100 million at 1998 prices in the most optimistic of circumstances. This, together with the adaptation of the vaccine to developing-country populations, would add at least another 6 years to the time required for development.

The risk of investing in adaptation and additional testing could be reduced if a firm waited until the results of the efficacy trial from the first population were available. Unfortunately, this sequential approach would lead to a prolonged period during which an AIDS vaccine would be available in industrialized countries but not in developing countries. An aggressive effort would test and adapt many AIDS candidate vaccines in parallel (1, 6). However, relatively few companies were pursuing multiple options and a number of approaches appeared to have been shelved before their potential value had been determined. The additional development steps needed to make a vaccine rapidly available for global use kept lengthening the time frame for vaccine development and increased the costs. Historically, vaccines reach affordable prices only when the market matures, creating competition and overcapacity and thus a willingness to sell at marginal prices. There is minimal investment in research and development or capacity to serve developing countries, and the public sector has shown little willingness to finance such investment either directly or by purchasing vaccines at prices that cover the full costs. The penalty has been slow development of new products and 10–15-year delays before their prices drop low enough to be affordable in the poorest countries. New paradigms of industry engagement in the research and development and commercialization of vaccines have to be introduced if this situation is to be rectified.

Balancing risk and reward

The firms participating in the survey noted that, in the early stages of vaccine development, corporate decisions were heavily biased towards reducing the risk in development rather than towards increasing the potential reward. The following three reasons were given to explain why increasing the future market reward alone would not increase the investment that companies were willing to take. First, some companies perceived the absolute probability of successful development of a vaccine as too low, making the size of the reward irrelevant. Second, for most companies the perceived time to commercial revenue was so long that the reward was heavily discounted and not the primary driver of decision-making. Third, sales to developing countries were driven by sales to the public sector, which had been slow to adopt other new products, e.g. hepatitis B and *Haemophilus influenzae* type B vaccines. Assurances about the future market for an AIDS vaccine therefore lacked credibility.

Raising private investment in AIDS vaccine development

The AIDS Vaccine Task Force identified a menu of mechanisms with potential to accelerate AIDS vaccine development (4, 5). The respondents in the industry study were asked to evaluate the likelihood of success of these mechanisms in accelerating investment in research and development for an AIDS vaccine. The mechanisms can be classified as push strategies, reducing the risks and costs of investment, and pull strategies, assuring a future return (Box 2).

Given the early stage of AIDS vaccine development, it is not surprising that the firms favoured push options that would directly subsidize research and development and manufacturing capacity. They also stressed the importance of working with developing countries with stable political environments, respect for intellectual property rights, and a strong national commitment to testing a vaccine that might benefit the population. Biotechnology firms, in particular, were far more interested in push mechanisms than pull mechanisms.

The larger firms noted that a viable developing country market was still an important consideration and that pull mechanisms would become critical once the scientific problems had been solved. These firms noted that increased purchase of other new vaccines would be the most credible strategy for stimulating greater investment in future products. Most companies supported tiered or differential pricing as a strategy for ensuring more rapid affordability in all markets. However, some firms in the USA expressed concern that consumers and/or the USA Government might not agree that other countries be offered a particular product at a greatly reduced price, even if they were among the poorest in the world. Several

Box 2. Potential push and pull mechanisms to accelerate the development of AIDS vaccines

Push strategies

- **Strengthening capacity in developing countries**

This involves investment in building national capacities and infrastructures of developing countries for applied vaccine development, notably clinical trials, making the countries better partners for vaccine development, reducing the costs of research and development, and improving the scope for efficacy trials.

- **Financing efficacy trials in developing countries**

Financial support enables developing countries to participate as partners with industry in trials of candidate vaccines vetted by international scientific review, helping to accelerate the global development of a viable product, either through the discovery of a successful AIDS vaccine or, in the event of failure of the vaccine, by increasing the understanding of the virus and vaccine approaches.

- **Financing of manufacturing capacity**

This would diminish reluctance to invest early in capacity that might be wasted if the vaccine efficacy trial failed.^a

Pull strategies

- **Increasing uptake of existing vaccines**

Many firms remarked that the best way to attract investment for future product development was to establish commercially attractive markets in developing countries for established vaccines, e.g. hepatitis B and *Haemophilus influenzae* type B vaccines.

- **Differential (tiered) pricing for developing country markets**

Differential pricing, or different prices for different markets, would enable industry to recover its investment in research, development and capacity in the markets of rich countries while offering the vaccine at low prices in poor countries (7, 8). If firms were limited to charging one price they would charge a high price that only rich countries could afford. Differential pricing is used for vaccines used routinely throughout the world, but has usually evolved over 10–20 years as the products matured (7).

- **Market guarantee mechanisms**

A future market could be guaranteed through financing mechanisms, such as contingent loans to developing countries for the purchase of an AIDS vaccine, or trust funds mobilizing support from the global community to purchase AIDS vaccines for the poorest countries (5, 9). Financing would only become available through these mechanisms if a product meeting certain predetermined criteria were developed, with a view to ensuring that the vaccine was safe, effective, and affordable in developing countries. These mechanisms might cover the full price of the vaccine or a flat subsidy per dose.

- **Prize**

A significant monetary or humanitarian prize could be offered to the first firm to develop an AIDS vaccine meeting certain criteria. However, the existence of a prize would not ensure either production or purchase of the vaccine.

- **Transferable patent extensions**

A firm could be given the right to extend the patent of any one product in its portfolio in markets of several large industrialized countries by a year or more, provided that it licensed or produced an AIDS vaccine meeting specific criteria of safety, effectiveness, and affordability in developing countries. This could be worth several hundred million US dollars to major pharmaceutical companies, thus causing a trickling down of investment to smaller biotechnology firms.

^a Since investment in production capacity spans the transition from scientific to market barriers, several respondents noted that effective pull mechanisms might be adequate for encouraging industry to absorb this risk.

respondents remarked that differential pricing would require safeguards to ensure that vaccines were not re-exported at reduced prices to wealthy markets. Firms also cautioned that, unlike many of the current vaccines costing less than US\$ 0.10 per dose, the lowest price at which an AIDS vaccine could be offered was likely to be several dollars per dose because of higher development and manufacturing costs. Transferable patents were supported, particularly by pharmaceutical firms with large, profitable portfolios. It was felt that a prize for the development of an AIDS vaccine would have little impact. Pharmaceutical firms were in business to develop and sell products, not to win prizes.

Conclusions

Accelerating the development of an AIDS vaccine for global use requires skills and finance from the public and private sectors and the industrialized and developing countries (10). At present, both the public and private sectors are underinvesting and much existing investment can benefit poor countries only indirectly and in the long term. This is not surprising, since the technology for an AIDS vaccine and for AIDS prevention more generally is a global public good: the benefits extend beyond national borders and people who are vaccinated reduce the probability of transmission to those who are not. This means that the private sector cannot reap many of the benefits of its investments, and that national governments have little incentive to invest in vaccines for strains of the virus and for people outside their borders.

The rapid development of vaccines against deadly diseases requires the public sector to understand the obstacles to increased private investment and to support the most efficacious solutions for overcoming them. The World Bank, the European Commission, WHO, UNAIDS, and other donors are currently considering the costs, benefits, and implementational issues of a broad menu of incentives for raising private investment to cover research into and development of an AIDS vaccine (2, 11). The views of industry provide an important insight into the combination of policies most likely to have an impact. Both push and pull strategies are necessary, although empirical evidence is still lacking on their effectiveness in both increasing investment and reducing development time. At the present early stage of AIDS vaccine development, scientific uncertainty is the most important reason given for low private investment. It is not surprising, therefore, that most firms favour push strategies that would subsidize development costs and reduce risk.

In the near future, however, the bottlenecks will shift from science to market. One of the most important market signals is the uptake of recently developed vaccines in low-income countries. International donors, private foundations, and WHO have recently renewed their commitment to communicable disease control by expanded coverage of

childhood vaccination, particularly through the Global Alliance for Vaccines and Immunization (12–15). In addition, the World Bank and its partners are exploring ways of using its lending facilities, potentially in conjunction with grant money, to provide a credible low-cost mechanism for ensuring the availability of funds for purchasing AIDS vaccines for poor countries.

The AIDS Vaccine Task Force has consulted extensively with policy-makers, scientists and non-governmental organizations in developing countries. This has underscored the critical role of developing countries themselves in reaching a political consensus and forging international public–private partnerships for the local testing and development of candidate vaccines in the interest of their populations. While various mechanisms can be expected to raise both public and private investment in the development of AIDS vaccines, the actions, commitment, and

leadership of the developing countries most affected by the AIDS epidemic are equally, if not more important. ■

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Conflicts of interest: none declared.

Résumé

Investissement privé dans la mise au point d'un vaccin contre le SIDA : obstacles rencontrés et solutions proposées

La mise au point de vaccins destinés à la prévention du SIDA, du paludisme, de la tuberculose et d'autres maladies exige des investissements à la fois publics et privés. Cependant, l'investissement privé a été bien inférieur à ce que l'on aurait pu espérer vu le grand nombre de personnes victimes de ces maladies, en particulier dans les pays les plus pauvres. Pour mieux comprendre la situation et chercher d'éventuelles solutions, le groupe spécial Vaccin contre le SIDA de la Banque mondiale a commandé une étude sur les perspectives qu'offrent les secteurs de la biotechnologie, des vaccins et des produits pharmaceutiques concernant l'investissement dans les travaux de recherche et de développement d'un vaccin contre le SIDA. On s'est ainsi aperçu que différents obstacles venaient entraver la mise au point d'un vaccin contre le SIDA au cours du cycle de

développement des produits. Pendant les premières phases, c'est-à-dire avant d'obtenir confirmation de l'intérêt que présente le produit, les principaux obstacles sont scientifiques. L'absence de consensus sur la méthode susceptible d'être efficace a multiplié les incertitudes et augmenté les risques qu'il y avait à investir dans des essais cliniques coûteux. Dans les phases suivantes, qui consistent à adapter, à tester et à produire à grande échelle le vaccin pour différentes populations, ce sont des aspects liés au marché qui ont pris le pas. Pour pouvoir augmenter le niveau des contributions privées consacrées à la recherche et au développement d'un vaccin contre le SIDA, il faudra probablement associer des mesures dissuasives (stratégies *push*), visant à réduire le coût et le risque scientifique de l'investissement, à des mesures incitatives (stratégies *pull*), qui garantissent un marché.

Resumen

Inversión privada en el desarrollo de vacunas contra el SIDA: obstáculos y soluciones

El desarrollo de vacunas para la prevención del SIDA, el paludismo, la tuberculosis y otras enfermedades requiere inversiones tanto del sector público como del sector privado. Las inversiones privadas, sin embargo, han sido mucho menores de lo que exige el enorme tributo en vidas humanas que se cobran esas enfermedades, sobre todo en los países más pobres. A fin de examinar esa situación y estudiar posibles soluciones, el Grupo Especial sobre Vacunas contra el SIDA, del Banco Mundial, encargó un estudio sobre las perspectivas de las empresas de biotecnología, de producción de vacunas y de productos farmacéuticos en lo que atañe a las inversiones en actividades de investigación y desarrollo orientadas a obtener una vacuna contra el SIDA. Se observó que durante el ciclo de desarrollo de los productos surgían diferentes obstáculos al desarrollo de una vacuna contra el

SIDA. Durante las fases iniciales, antes de verificar la eficacia del producto, los principales obstáculos eran de naturaleza científica. La falta de consenso respecto al enfoque con más probabilidades de resultar eficaz aumentaba la incertidumbre y el riesgo asociado a la inversión en costosos ensayos clínicos. Las últimas fases, relacionadas con la adaptación, el ensayo y la ampliación de la producción para distintas poblaciones, eran las más influidas por las consideraciones sobre la situación del mercado. A fin de aumentar la contribución del sector privado a las actividades de investigación y desarrollo de vacunas contra el SIDA, habrá que dar probablemente con una combinación de estrategias impulsoras (*push*), para reducir los riesgos económicos y científicos de las inversiones, y estrategias atractoras (*pull*), a fin de garantizar un mercado para el producto.

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