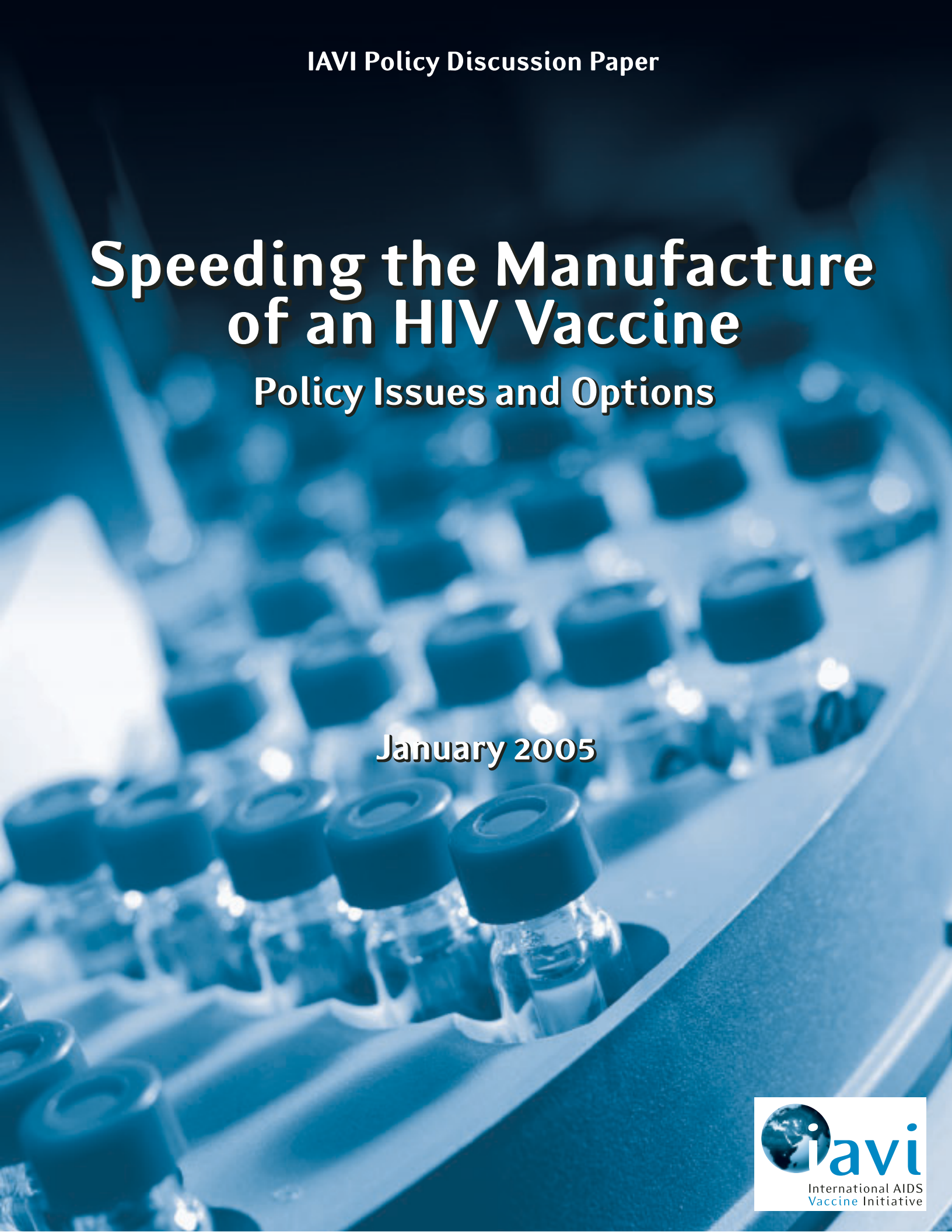
IAVI Policy Discussion Paper

Speeding the Manufacture of an HIV Vaccine

Policy Issues and Options



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International AIDS Vaccine Initiative

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Contents

Executive summary *v*

Introduction *vii*

Definitions

1 HIV vaccine manufacturing *1*

HIV vaccines: a failure of business as usual 1
HIV vaccine development: new developers, new roles, new challenges 1

2 Making and testing a vaccine: bioprocess development *3*

Bioprocess development: the product is in the process 3
Clinical materials 4
Policy options to improve bioprocess and clinical materials production capacity 5

3 Large-scale manufacturing for future HIV vaccines *8*

Launching a vaccine: recouping financial investments 8

4 Conclusion *13*

Appendix 1 Phases in vaccine clinical trials *14*

Notes *16*

References *18*

Executive summary

While expanding existing prevention and treatment programs is crucial to slowing the spread of HIV and to prolonging and improving the lives of people living with HIV, they will not by themselves be sufficient to bring an end to the epidemic. To do this, a safe and effective HIV vaccine is needed.

Important progress is being made in the search for HIV vaccines. Investment has increased considerably in recent years, with research and development now being conducted by researchers from academic, not-for-profit, public and private institutions.[1] More than 30 vaccine candidates are currently being tested, the majority in small early stage clinical trials.[2] While this is encouraging, the ever-growing scale of the HIV epidemic requires that these efforts are intensified and accelerated. Speed is crucial—delays will cost millions of lives.

The growing vaccine clinical pipeline is encouraging. However, without a fully developed manufacturing process and a plant in which to implement it, even the most clinically effective HIV vaccine will have little or no impact on the global HIV epidemic.

There are two serious barriers to timely and efficient manufacturing of HIV vaccines. One is that most HIV vaccine developers work in academic institutions or small companies that lack access to the funding, expertise and specialized facilities to develop processes to manufacture promising vaccine candidates and to produce small lots of vaccine for trials (referred to in this paper as the "product development" challenge). This failure to integrate clinical development with bioprocess development is causing delays and inefficiencies in the HIV vaccine R&D pipeline. If left unaddressed, these inefficiencies will lead to major bottlenecks in the coming years, as an increasing number of HIV vaccine candidates move forward for clinical testing.

The second looming barrier, while still a few years away, is that investments in the manufacturing capacity needed to supply widespread vaccine use will be severely delayed due to high levels of scientific uncertainty connected with HIV vaccine development and financial risks associated with launching a new vaccine in developing countries. This challenge is compounded by the fact that most HIV vaccine developers have no experience with large-scale manufacturing and will require industry partners. Together, these problems comprise what this paper refers to as the "large-scale manufacturing" challenge.

Although the poor countries of Africa, Asia and the Americas urgently need an HIV vaccine, they have weak purchasing power. Investors do not regard these countries as providing a sufficiently viable market to justify early investment in HIV vaccines or manufacturing capacity to meet developing country needs. Without such investment and capacity the introduction and use of a successful HIV vaccine will be seriously delayed in countries where it could save the most lives. The experience with other new vaccines over the past three decades (such as the Hepatitis B vaccine) suggests that the delays could be as long as 15 years or more. Such a delay in introducing an HIV vaccine, in Africa and Asia in particular, would be catastrophic.

Public sector intervention can mitigate these process development and large-scale manufacturing challenges and speed the discovery, production, and worldwide distribution of an HIV vaccine.

In this paper, we describe the main manufacturing issues in product development and explain why they are slowing down the development of an HIV vaccine. We set out a number of policy options to address these issues. We go on to outline the future challenges to large-scale

More than 30 vaccine candidates are currently being tested, the majority in small early stage clinical trials

manufacturing and propose a number of options to address them, too.

We believe that among the policy options laid out in this paper, several stand out as being promising and should be more deeply explored in the coming months. They include the idea of creating a virtual bioprocess development group, extending special financial assistance to vaccine developers to purchase bioprocess services, financing measures to help expand the availability of bioprocess capacity and the plan to construct and staff a dedicated bioprocess facility for vaccines to address the major diseases of the developing world, especially HIV.

Several policy options stand out as being promising and should be more deeply explored in the coming months

The policy options in this paper now need to be thoroughly debated and acted upon swiftly by developing country governments, international development donors and industry. As a matter of urgency, key stakeholders in the HIV vaccine field must now work together to set priorities and develop concrete proposals to present at the G8 summit in July 2005, which will consider plans to establish and support a Global HIV Vaccine Enterprise.

Introduction

In the 20 years since HIV was identified as the cause of AIDS, the pandemic has grown to be the world's greatest public health crisis. More than 60 million people have been infected with HIV, and 15 million have died. Each day another 14,000 people are infected, more than 5 million people each year.

More than 30 vaccine candidates are now being tested, the majority in small, early stage clinical trials.[3] While this is encouraging, the ever-growing scale of the epidemic requires that these efforts are intensified and accelerated. Speed is crucial. Delays will cost millions of lives.

Despite these considerable investments, the HIV vaccine field faces two significant barriers that may limit the speed of progress. One is the lack of access to funding, expertise and specialized facilities to develop processes to manufacture promising vaccine candidates. This is causing inefficiencies in vaccine development and testing. If left unaddressed, there is a risk that the inefficiencies will become major bottlenecks in the next few years as more HIV vaccine candidates move forward for clinical testing.

A second manufacturing barrier is further threatening to obstruct the launch of a future HIV vaccine. Today's scientific uncertainties make it risky to invest in establishing manufacturing facilities in time for an early product launch. Market conditions create further disincentives to building facilities to supply a vaccine for use by developing countries. Although these countries most need an effective HIV vaccine, there is uncertainty about their having access to the funds to purchase and deliver one. Unless these scientific and financial risks can be mitigated, early investments in manufacturing capacity will not take place, substantially delaying the use of a successful HIV vaccine, particularly where it could save the most lives.

Public sector intervention is thus required to overcome these two challenges for process development and large-scale manufacturing. Such intervention, including increased public sector investment, would accelerate the development and future introduction of an HIV vaccine in developing countries, paying great returns in averted infections.

Fortunately, the need for action to address the manufacturing challenges is now on the political agenda. In 2003 a group of leading HIV vaccine developers proposed a Global HIV Vaccine Enterprise to facilitate collaboration, address strategic challenges and accelerate HIV vaccine development.[4] With manufacturing identified as a key issue, a working group was established to identify problems and propose solutions.[5] At their 2004 summit in the United States, G8 leaders endorsed the call to establish a Global HIV Vaccine Enterprise, with specific mention of manufacturing and challenges in the communiqué.[6]

This paper contributes to the debate on manufacturing. It describes the main issues in process development and explains why they may slow the development of HIV vaccines. It next sets out policy options to address the issues. It goes on to outline future challenges to large-scale manufacturing, again proposing options to address these challenges. The paper is intended for a nonspecialist audience. As many of the issues addressed are technical, a brief definition of terms follows along with a diagram showing the interlinked processes essential for developing, testing and successfully launching a new vaccine (figure 1).

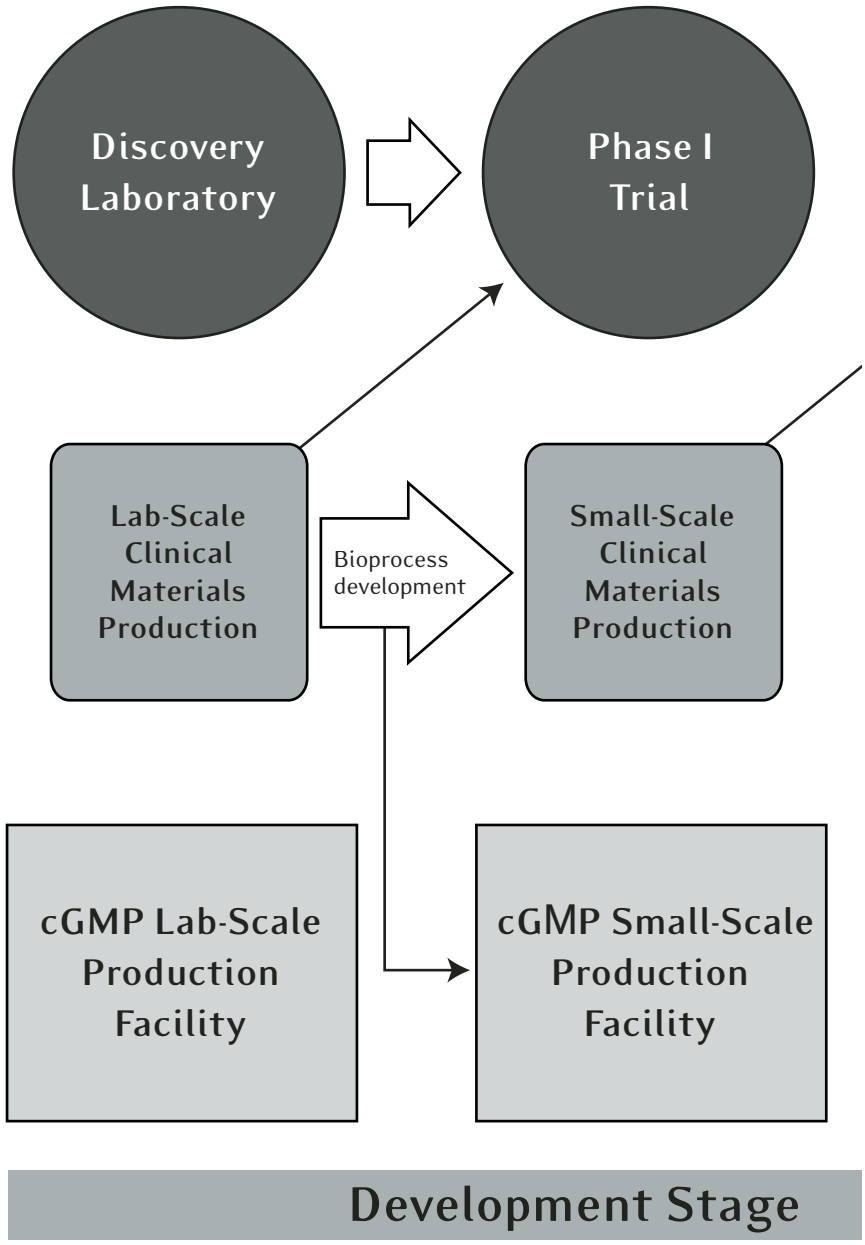
FIGURE I

Phase I Trial
Small studies (10s of participants) testing safety and initial immunogenicity

Clinical Trials
A series of increasingly large empirical studies that provide data on vaccine safety, immunogenicity and efficacy. Clinical data also provide key parameters that partly determine the practicality and economic viability of large-scale vaccine production.

Bioprocess Development
The progressive design, implementation and testing of the processes required to manufacture a particular vaccine at increasingly large-scales. Work is undertaken in bioprocess development facilities of increasing sizes. Processes are then transferred to manufacturing facilities for implementation. Outputs include, a fully defined process, analytical tools needed to show vaccine and process consistency and quality, empirical evidence of process robustness and design specifications for manufacturing facilities.

Manufacturing Facilities
As vaccine development progresses increasing volumes of vaccine are required that have been manufactured under cGLP and then cGMP standards. Small-scale facilities are capable of being fitted out to produce batches of different vaccines. Large-scale manufacturing facilities are designed for the most efficient possible production of a single vaccine. Designing, building and validating a large-scale manufacturing facility takes a minimum of four years and cost hundreds of millions of dollars.

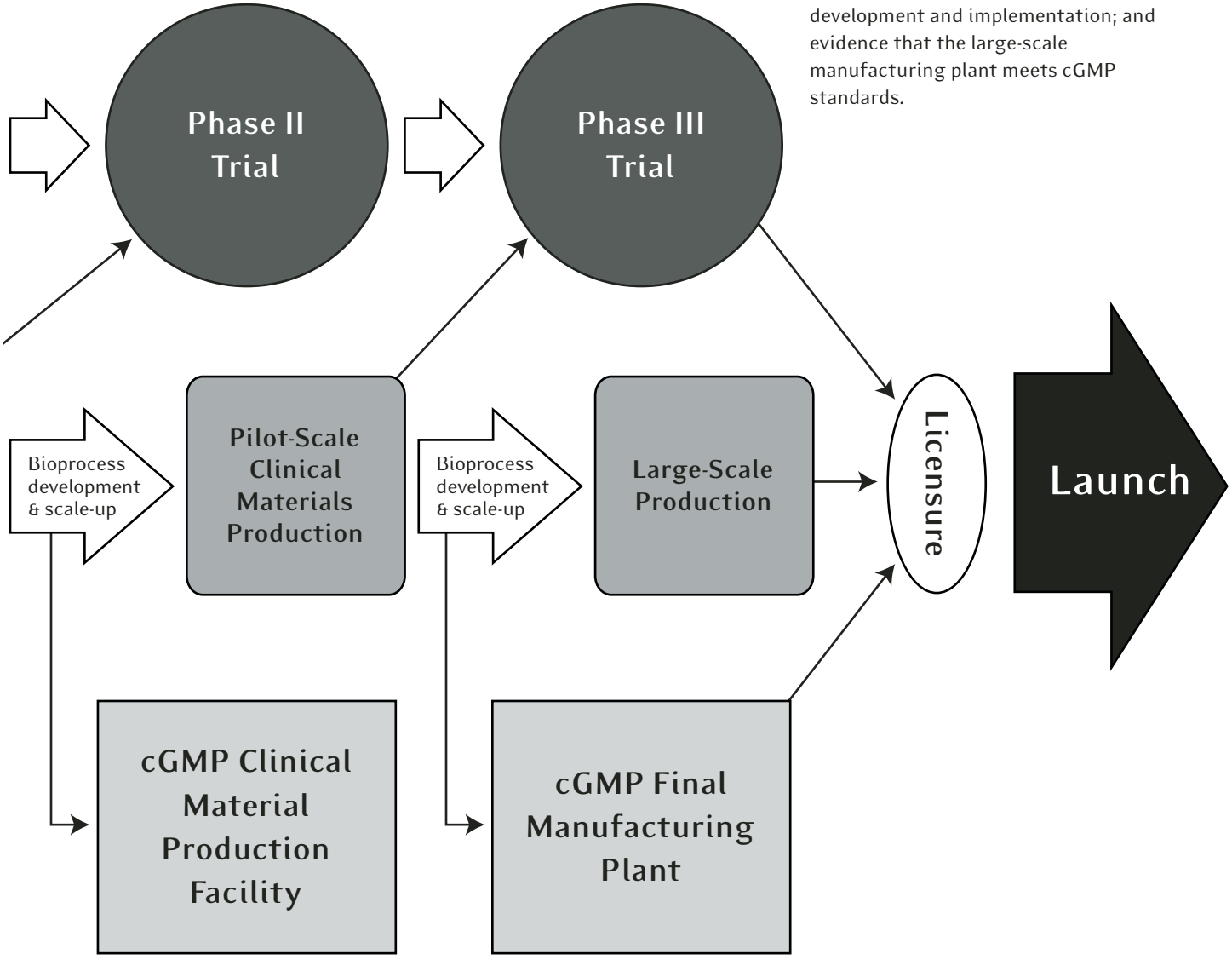


Clinical Materials Manufacturing Facilities
Clinical materials are manufactured at increasing scales as trials progress. At smaller scales, production suites in existing facilities may be fitted with standardized, often disposable, equipment. At large scales, equipment is usually custom-made and facilities specially constructed.

Phase II Trial
Medium size studies (up to 100s of participants) testing immunogenicity

Phase III Trial
Large study (1000s of participants) testing vaccine efficacy

Licensure
For licensure, regulatory authorities require evidence of vaccine safety and efficacy from clinical trials; evidence of a robust and consistent large-scale manufacturing process from bioprocess development and implementation; and evidence that the large-scale manufacturing plant meets cGMP standards.



Manufacturing Stage

Pilot-Scale Manufacturing
Phase III trials should be conducted with test vaccines produced by the same process and at approaching the same-scale as will be used to manufacture vaccines for general use.

Current Good Manufacturing Practice (cGMP)
cGMP defines a set of standards for procedures and facilities required by regulatory authorities for pilot- and large-scale manufacturing of vaccines for use by humans.

1 HIV vaccine manufacturing

Academic and public institutions typically have conducted the basic science research to identify promising vaccine concepts in the laboratory. Product development—taking promising ideas and turning them into viable commercial vaccines—has largely been the remit of the private sector. Where market prospects are attractive, large R&D-based companies have done the clinical testing, bioprocess development, manufacturing facility construction and commercial launch of new vaccines.

Vaccine development requires scarce technical resources and hundreds of millions of dollars. To minimize the risks and get the most from these investments, companies set priorities for the most scientifically and commercially promising candidates—accelerating them through development and launching new vaccines quickly. For this, large R&D-based companies generally adopt an integrated approach that brings together in-house all the technical expertise, facilities and human resources required.[7] This gives control over the timing and sequencing of interrelated activities, allows strict attention to quality and enables more efficient management and transfer of expertise, knowledge and technologies. The approach closely links clinical testing with bioprocess and clinical materials production, all of which are needed to develop and test an efficacious vaccine that can be reliably and economically manufactured at large scales.

A commercial imperative for vaccine companies is to launch a new vaccine as rapidly as possible and to begin making returns on the large R&D investments. That is why they target predictable, high margin, relatively low volume markets in developed countries. There has typically been a delay of 15–20 years before a vaccine launched in developed countries is available for widespread use in developing countries.[8]

HIV vaccines: a failure of business as usual

Although scientists agree that developing an HIV vaccine is possible, given enough resources and commitment, several difficult scientific challenges remain. Researchers do not yet know what type of immune response is required to protect against HIV infections or what kind of antigen will elicit such a response.[9] No validated model can predict successful vaccination in humans on the basis of laboratory or animal testing. Confirming a vaccine's efficacy is possible only after large, time-consuming and expensive clinical trials.

In addition to the scientific uncertainties, companies face a financial barrier. Developing country markets require high production volumes and have been built on low prices. That weakens the financial incentives for companies to launch an HIV vaccine in Africa, South Asia and other poor regions.

As a result, none of the five major R&D-based vaccine companies—Aventis Pasteur, Chiron, GlaxoSmithKline, Merck, Wyeth-Lederle, which account for over 80% of the global vaccine market by sales value—have made HIV vaccine development a commercial priority.[10, 11]

HIV vaccine development: new developers, new roles, new challenges

Given the limited investments of the big five vaccine companies in HIV vaccines, academic groups, public agencies, small private developers and not-for-profits have stepped in, extending their activities beyond their usual work in basic science into clinical testing and product development. But these developers lack in-house access to the full range of

Vaccine development requires scarce technical resources and hundreds of millions of dollars

expertise and facilities required for bioprocess development, clinical materials manufacturing capacity and large manufacturing facilities. They also usually lack the financial resources to adequately contract for (or invest in) such essential work.

Where funding is available, HIV vaccine developers have relied on a variety of external contractors to provide services for bioprocess development and clinical materials manufacturing. But the range of contract services and capacities is limited—and not well matched to the demands of an HIV vaccine. Some developers, particularly those exploring vaccines that require a combination of technical approaches, have had to contract with several external providers to obtain all of the services they require, adding to management and logistical difficulties.

The bottlenecks facing the small vaccine developers are likely to get worse in the next few years. This could result in wasted efforts on vaccine candidates later shown unsuitable for manufacturing on a large scale—and delays in transferring promising candidate vaccines from the laboratory to clinical testing. Equally, unless large vaccine companies engage in the HIV vaccine field, there will be a crisis in the large-scale manufacturing of successful vaccines in the future. (Table 1 summarizes access to different types of bioprocess development and manufacturing expertise and facilities for a range of HIV vaccine developers and potential contract organizations.)

Public action is needed to address these problems through political commitment, policy changes and appropriate financing. Public intervention and investment now will help accelerate HIV vaccine development and lay the foundation for faster access to affordable HIV vaccines in developing countries.

TABLE 1

	In-house activities			
	Bioprocess development	Small-scale manufacturing (cGMP)	Pilot-scale manufacturing (cGMP)	Large-scale manufacturing (cGMP)
Developers				
Large R&D-based vaccine companies[a]	**	**	**	**
Biotechnology companies[b]	*	*		
National research agencies[c]	*	*		
Academic institutions[d]	*	*		
Not-for-profit initiatives[e]	(*)	(*)		
Potential external contractors				
Contract manufacturing organizations[f]	*	**	*	
Process development labs[g]	**	*		
Developing country manufacturers[h]			*	**

* Less capacity

** More capacity

(*) Provide funding, project management support and access to clinical trial infrastructure to research partners, usually biotechs or academic institutions.

Note: cGMP means good manufacturing practice standards.

a. Such as Aventis Pasteur, Chiron, GlaxoSmithKline, Merck and Wyeth-Lederle.

b. Such as VaxGen and AlphaVax.

c. Such as the National Institutes of Health (United States), Agence Nationale de Recherches sur La SIDA (France), Medical Research Council (United Kingdom), Indian Council for Medical Research (India) and Medical Research Council (South Africa).

d. Such as John Hopkins University (United States), Karolinska Institutet (Sweden), University of Nairobi (Kenya), Uganda Virus Research Institute (Uganda), Instituto Superiore di Sanità (Italy) and University of Oxford (United Kingdom).

e. Such as the International AIDS Vaccine Initiative and the South African AIDS Vaccine Initiative.

f. Such as Cobra and IDT.

g. Such as BioReliance Corporation (United States/United Kingdom) and Transgene (France).

h. Such as the Serum Institute of India.

2 Making and testing a vaccine: bioprocess development and clinical materials

Vaccines are defined both by their biochemical composition and by the process for manufacturing them. To grant a license for a new vaccine, a regulatory authority requires:

- Evidence from clinical trials of vaccine safety and efficacy.
- Evidence showing that a manufacturing process has been developed that can consistently produce the vaccine in accordance with strict regulatory standards and at the scale needed to supply general use.
- Evidence that the manufacturing facility in which this process is to be implemented also meets current good manufacturing practice (cGMP) standards.[12]

These requirements make it imperative that clinical testing, bioprocess development and the progressive scaling up of a manufacturing process for a candidate vaccine proceed together and are closely linked (see figure 1).

Bioprocess development: the product is the process

Bioprocess development brings together the disciplines and skills of chemical and mechanical engineering, biochemistry and microbiology to design, implement and demonstrate that a manufacturing process for a particular vaccine works consistently and economically at progressively larger scales. Increasing the scale of a manufacturing process is not just a question of more ingredients and bigger equipment. Many manufacturing processes vary in nonlinear ways as scale is increased. As a result, something that works with small volumes in a laboratory may not work at scales many thousands of times larger needed to manufacture a vaccine for general use.

This variability means that an essential output of bioprocess development is a range of analytic tools to prove that the vaccine produced at each increased scale is the same product and is manufactured reliably to stringent standards of consistency and purity. While theoretical calculations can provide a guide, bioprocess development is an empirical and iterative discipline requiring access to specialist facilities, as well as considerable highly specialized technical knowledge, experience and practical know-how. Access to bioprocess expertise is a key proprietary asset for vaccine companies.

Initial bioprocess development should begin before a promising vaccine candidate enters clinical testing and then continue in tandem with its progression through the different phases of clinical trials. Not all promising candidate vaccines will be economically manufacturable at the scales needed for general use. Early bioprocess development is thus an important tool to help set priorities for the progression of different vaccine candidates into and through clinical development. As trials progress, important clinical data, such as dose levels and vaccination schedules, must be fed into bioprocess analysis because they provide basic parameters for the calculation of required process yields (the scale of production needed to produce a certain number of doses). Mutually interdependent, bioprocess development and clinical testing should be closely linked.

Although different vaccines may use the same technologies or the same manufacturing processes (table 2), each requires specific bioprocess development. While experience with similar technologies or processes can provide important guidance, individual attention for each vaccines is required to:

- Optimize manufacturing efficiencies.
- Develop and validate suitable analytical tools.
- Refine design specifications, process yields and process implementation.

Access to bioprocess expertise is a key proprietary asset for vaccine companies

TABLE 2
HIV vaccine technologies and manufacturing processes

Technology	Manufacturing process
Recombinant viral vectors	Cell-culture (such as Adenovirus, Merck) Egg-based primary cell culture (such as Modified Vaccina Ankara, IAVI)
Recombinant subunit vaccines	Microbial fermentation
DNA vaccines	Microbial fermentation (such as HIVA, IAVI)

Note: Combination vaccine approaches, such as DNA-MVA prime boost strategies, may require access to more than one manufacturing process.

Ideally vaccine developers should bring bioprocess development and clinical materials production under the same roof and link the staff undertaking them

- Empirically demonstrate manufacturing robustness and consistency to regulatory agencies.

At large scales of production, small differences in yields or manufacturing efficiency can have a major impact on unit costs. Getting the process right for a particular vaccine is crucial to its profitability—or for vaccines for use in developing country settings, to its affordability.

Clinical materials

The clinical testing of a candidate vaccine involves several phases (appendix 1). Phase I and II trials are designed to look at the candidate's safety and immunogenicity in up to a few hundred people (for Phase II trials). If results from these tests are promising, the candidate may be taken into much bigger and more expensive Phase III efficacy trials involving many thousands of participants. For trials to take place, timely and sufficient volumes of the vaccine ("clinical materials") must be available. For use in human trials, clinical materials must be manufactured under cGMP conditions. Bioprocess development must define a process suitable for the scale of production required for a trial—and to provide the validated analytical tools to demonstrate the identity, consistency and quality of the vaccine (to show that the same thing is being tested in subsequent trials).

Manufacturing clinical materials using increasingly large processes provides important practical data and experience with the processes developed in bioprocess facilities. Importantly, licensing requires that the vaccine used in a Phase III trial is manufactured by the same process and approaching the same scale as the product to be launched for general use. Clinical materials for Phase III trials should be produced in a pilot-scale facility capable of implementing the final manufacturing process within a 10-fold scale of that for the future production of the product.[13]

Ideally vaccine developers should bring bioprocess development and clinical materials production under the same roof and link the staff undertaking them. This helps facilitate effective transfer of technologies and knowledge from bioprocess development to clinical materials production and vice versa. Bringing clinical materials production in-house also provides more control over the quality and timing of batches.

The use of external contractors can present logistical difficulties. First, the necessary bioprocess expertise and manufacturing capacity may not be available from one provider, resulting in the need for multiple contractors and potential inefficiencies in transferring technologies and knowledge. Second, booking production slots for external contracts requires lead times of up to two years. Slippage in the progress of clinical testing can mean missed slots and further delays. Third, external contracting requires considerable oversight to maintain a high quality of materials produced.

Current bioprocess and clinical materials constraints

Between 2000 and 2004 the number of HIV vaccine candidates in small human trials doubled.[14] In 2003, 19 new HIV vaccine trials were initiated involving 18 vaccine candidates, bringing the total number of HIV vaccines in trials to more than 30.[15] Over the next three to five years, the number of candidate vaccines in clinical trials and the number of trials are both expected to increase. On current timelines, up to three vaccine candidates may, if the results of prior trials are promising, enter larger studies

investigating efficacy in the next three years. Demand for clinical materials for HIV vaccine trials is thus likely to rise. Demand from other vaccine fields, such as tuberculosis and malaria, is also rising.

A recent IAVI survey of vaccine developers and manufacturers confirms serious gaps in bioprocess development and clinical materials production capacity suitable to support HIV vaccine development.[16] Of 330 organizations contacted, data were gathered from 274 contract manufacturing organizations, biotechnology firms, vaccine companies, academic institutions and process development laboratories. The survey showed that the capacity to undertake integrated bioprocess development and clinical materials production up to pilot scale does not exist outside of the large R&D-based vaccine companies. Small-scale manufacturing capacity suitable for different vaccines does exist in a range of contract manufacturing organizations and biotechs. But few have the capability to implement all steps in a large-scale manufacturing process or to work with more than one type of vaccine manufacturing process.[17] While there currently is excess capacity for processes based on microbial fermentation, capacity is more limited for live viral vaccines (cell line and egg-based systems).[18]

The survey confirms two key points:

- Most HIV vaccine developers lack in-house access to the bioprocess and clinical materials capacity required to develop a candidate vaccine.
- Some contract capacity for bioprocess development and clinical materials production does exist, but it is poorly matched to the needs of current HIV vaccine development.

Consequences for HIV vaccine development

There is anecdotal evidence that limited access to cGMP manufacturing capacity has delayed clinical trials. Increasing demand for clinical materials, both for HIV and for other vaccine products, is likely to make this worse. Developers pursuing multicomponent vaccine strategies, such as DNA-MVA prime-boost, and developers relying on more than one production process face particular difficulties. Although the discussion of particular cases is commercially sensitive, the recent decisions by some vaccine developers to establish their own small-scale clinical materials and bioprocess capacity—such as the National Institutes of Health (NIH) Vaccine Research Center[19] and St Jude's Children's Research Hospital[20] (neither dedicated solely to HIV vaccines)—reflect the difficulties experienced in accessing and managing contractors that can meet requirements for technology, quality, scale and timing.

There is also some anecdotal evidence that the difficulties and costs in accessing appropriate bioprocess expertise and clinical materials capacity can deter vaccine developers from bringing candidates into the clinical pipeline. Increasing the resources and capacity available for bioprocess development and clinical materials production capacity may thus act as an incentive to bring a wider range of candidate vaccines into clinical trials and facilitate greater opportunities for parallel testing, comparison and setting priorities. That would accelerate development while making more efficient use of research resources.

The capacity to undertake integrated bioprocess development and clinical materials production up to pilot scale does not exist outside of the large R&D-based vaccine companies

Policy options to improve bioprocess and clinical materials production capacity

To expedite progress on HIV vaccines, it is important that all product developers have flexible access to appropriate bioprocess development expertise and to clinical materials production facilities of high and consistent quality.

Policy options to address these needs fall into shorter (1–2 years) and longer (2–4 years) term measures, depending on the lead times necessary to implement them (table 3).

Shorter term options

1. Improve management of existing bioprocess and clinical materials production capacity (a virtual bioprocess and analytical development group)

- A dedicated team of bioprocess experts could be convened under contract to manage services and facilities on behalf of participating HIV vaccine developers. The group would bring together expertise in all necessary manufacturing processes and

TABLE 3
Summary of public policy options for HIV vaccine process development

	Expansion of capacity	Increased integration and efficiency	Timeframe to implement	Expected cost
Improve management of existing bioprocess and clinical materials production capacity (Option 1)	Low	Moderate	Short	Low
Increase financing to support contracting for bioprocess development (Options 2 and 3)	Moderate (may also mobilize investment from private sector)	Low	Short	Low to moderate
Invest in additional capacity (Option 4)	High	Moderate	Long	Moderate
Invest in public interest capacity (Option 5)	High	High	Long	High

vaccine technologies required by the field. The group could develop a database of existing contract capacity and take a hands-on approach to project management and quality control. In addition, by aggregating demand for bioprocess and clinical material production capacity, the group could command great market leverage for HIV vaccines.

2. Increase financing to support contracting for bioprocess development

- *Greater donor awareness of and funding for bioprocess development.* A variety of public sector and philanthropic donors already invest in HIV vaccine R&D. They could emphasize the importance of bioprocess investments with researchers and make additional resources available to support greater access to expertise, facilities and services.
- *Market rate or subsidized loans to vaccine developers.* The European Investment Bank, the World Bank's International Finance Corporation, the Overseas Private Investment Corporation, KfW and the Japan Bank for International Cooperation could be sources of loan capital to vaccine developers to help them buy process development services. In some cases, their eligibility requirements may need to be modified to enable the financial institutions to make loans to small companies and academic institutions based in developed countries.

  However, loans are less attractive than grants, particularly for public, academic or not-for-profit agencies, which may also be prohibited from using loan financing.
- Increased availability of resources for bioprocess development, particularly if combined with greater collaboration among vaccine developers (option 1), could enable contracting or other partnerships with a wider range of private sector companies (including the large R&D-based companies) than currently possible.[21]

Longer term options

3. Increase financing to support contracting for bioprocess development

- Given costs reaching tens of millions of dollars for bioprocess development, tax credits may prove useful for privately funded organizations. Ideally, bioprocess investments should qualify under a broader R&D tax credit, such as the 50% tax credit on R&D for AIDS, tuberculosis and malaria introduced by the UK government in 2003.[22]
- But tax credits are not enough by themselves. They may not be attractive to biotech companies as they may still require funds up-front for investment and often do not operate in profit during product development. One option could be to allow biotechs to hold and transfer tax credits if and when larger pharmaceutical companies acquire their technology. In addition, tax credits are complex to design and administer, and thus take time to establish if legislation is needed.

4. Invest in added capacity for individual organizations

- *Public sector institutions (such as the National Institutes of Health in the United*

States). Investment could be made in added capacity for bioprocess development and clinical material production capacity for major public research institutions. NIH has recently made investments in small-scale facilities, but these do not yet provide facilities to scale up processes or manufacture test vaccines at pilot scales.[23] Ideally, access to such facilities could be made available to external vaccine developers (which may require changes in regulations).

- *Private sector companies*. A mix of grants, soft loans and tax credits could encourage the private sector (biotechs, contract manufacturing organizations, developing country manufacturers) to invest in bioprocess development and clinical materials production appropriate to the needs of HIV vaccine developers. Public investment in private capacity would be conditional on preferential access to services for HIV vaccine developers (or other priority vaccines, such as those for tuberculosis or malaria).

5. Invest in public interest capacity for the HIV vaccine field

- A dedicated public interest facility could pull together all the skills, expertise and capacity needed to bring bioprocess development and clinical materials manufacturing to pilot scale, mimicking the approach of large R&D-based vaccine manufacturers. Such an approach could increase efficiencies in managing facilities, skills and knowledge generation. Public interest models are under development in other vaccine fields, such as new facilities being established by the International Vaccine Institute in the Republic of Korea.[24]
- Ideally, a public interest facility would be capable of taking several vaccine candidates from small to pilot-scale manufacturing in parallel. It would have the necessary bioprocess and analytical development skills, expertise and facilities to handle the three vaccine production technologies used by the current generation of HIV vaccine candidates—or a subset for those most needing added capacity.[25] The public interest focus of the facility could provide opportunities for innovative intellectual property management arrangements and the potential to share learning across different development programs (as where similar vaccine technologies or manufacturing processes are used). Such arrangements are more likely to be amenable to public sector and not-for-profit developers—the willingness of small private developers to utilize such a facility under a variety of intellectual property arrangements needs to be tested.
- Cost estimates for designing and building such a facility range from $60 million[26] to $300 million,[27] depending on the range of process technologies catered to and the scale of production possible.[28] Design, construction and validation would take at least three years.[29]
- Funders for such a facility could include philanthropic institutions, development banks and bilateral and multilateral donor agencies. The large investments would require a strong case demonstrating the long-term public health impacts and the substantial social and economic benefits.
- Further work is needed to develop a business model for such a facility, particularly to test demand for a facility and the options to ensure financial sustainability (operational costs are likely to be tens of millions of dollars a year). Robust and transparent governance and management arrangements will also be necessary if access to the facility is to be based on an assessment of the most promising HIV vaccine candidates.

A dedicated public interest facility could pull together all the skills, expertise and capacity needed to bring bioprocess development and clinical materials manufacturing to pilot scale

3 Large-scale manufacturing for future HIV vaccines

The rising costs of launching a vaccine, driven partly by more stringent regulatory requirements for vaccine production, mean that companies are cautious about making investments in manufacturing capacity

The launch and widespread use of a new vaccine requires a large validated cGMP vaccine manufacturing plant capable of reliably and consistently producing millions of doses of a vaccine, in strict accordance with regulatory requirements and at an economically viable cost. To maximize production yields and cost efficiencies, this plant will need to be designed for a particular vaccine. In addition, because vaccine manufacturing has fairly high fixed costs, scaling a facility as closely as possible to meet anticipated demand in the target markets is important to delivering low unit production costs.[30]

Launching a vaccine: recouping financial investments

A large-scale manufacturing plant can cost several hundreds of millions of dollars—on top of hundreds of millions of dollars that will have been spent on clinical testing and bioprocess development. To recoup investments as quickly as possible, companies launch new vaccines in the predictable high-value markets in developed countries. Although accounting for only 12% of worldwide vaccine sales by volume, developed countries account for 82% of the global vaccine market by revenue.[31]

The design, construction and validation of a large-scale manufacturing plant can take 4–6 years, depending on process and engineering specifications determined in bioprocess development. The long lead time to establish a manufacturing plant requires that investments in design, construction and validation begin well before final efficacy data are available if the vaccine is to be launched promptly. Ideally, design and construction will begin before the start of Phase III trials (figure 2).[32]

The rising costs of launching a vaccine, driven partly by more stringent regulatory requirements for vaccine production, mean that companies are cautious about making investments in manufacturing capacity until they have a reasonable level of confidence that the candidate will be licensable and that there is a large enough and profitable enough market. At a global scale, neither holds true for HIV vaccines today.

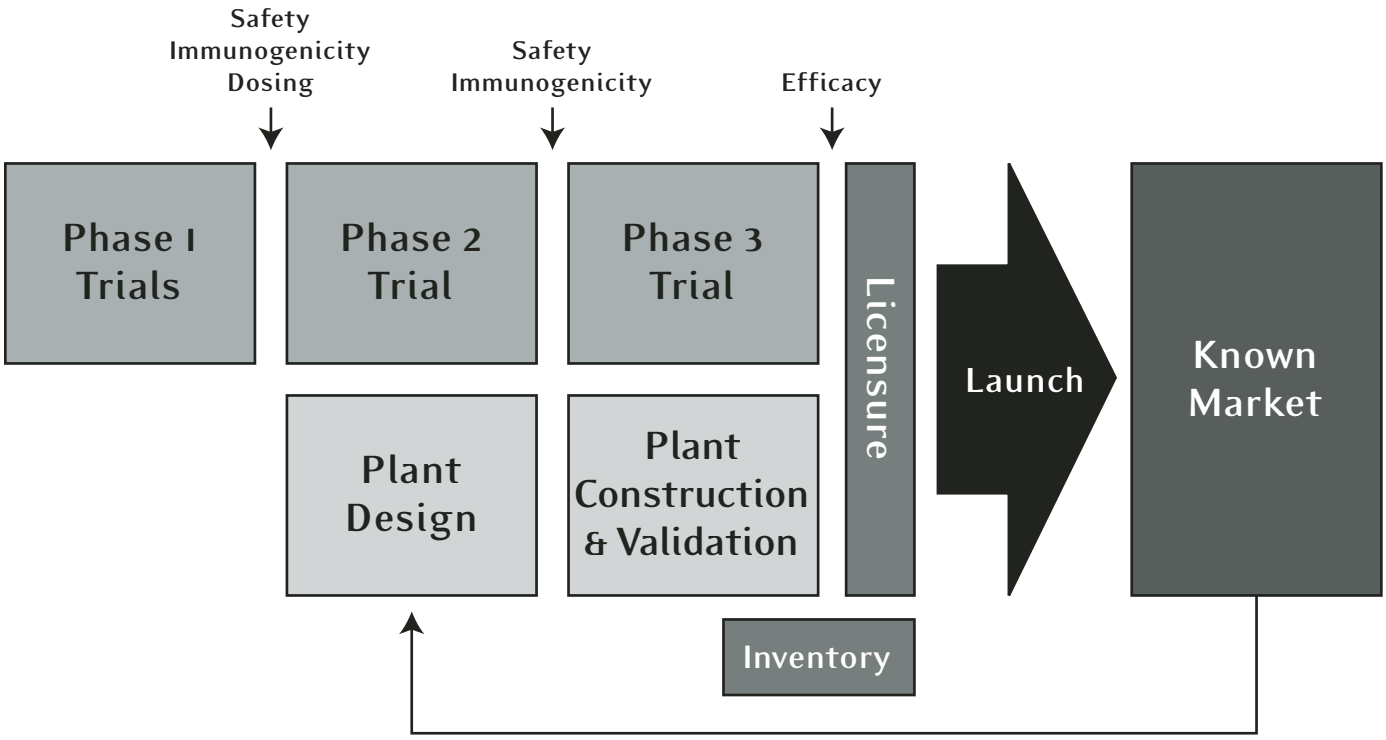
The enormous public health need in the developing world means that business needs to be done differently. Manufacturing capacity should be built to meet global demand and not just the demand of the developed world. But estimating global demand is difficult. Developing countries will to a considerable degree be reliant on the donor community to support vaccine purchases and deliveries.[33] No firm financing commitments have yet been made to guarantee a viable HIV vaccine market in developing countries.

Unless greater engagement by large-scale vaccine manufacturers in the HIV vaccine field can be secured, rapid widespread use of a future vaccine will be difficult to achieve. Few HIV vaccine developers have experience in large-scale manufacturing and vaccine launches.

Public policy options

Unless these challenges and risks are addressed, the launch of a future HIV vaccine could be delayed by several years in developed countries and even longer in developing countries. Public sector intervention could reduce or eliminate these delays in three ways. First, action could be taken to encourage early investment in HIV vaccine manufacturing capacity, by managing or sharing risks associated with scientific uncertainties. Second, the public sector could encourage early investment in manufacturing capacity to supply developing countries by managing risks associated with market uncertainties. Third, intervention could encourage

FIGURE 2



partnerships that bring to the field the expertise to establish manufacturing capacity and launch new vaccines.

1. Invest early in manufacturing capacity

- *Support trial strategies that manage scientific risks.* Standard approaches to clinical testing of a new vaccine proceed through three phases of clinical trials (see appendix 1). Data on vaccine efficacy is established in large Phase III trials, which require up to tens of thousands of participants and take several years to complete.[34] Waiting until data from such trials are available to initiate the construction of a manufacturing plant could delay the launch by several years.

  Recently, a number of vaccine developers have proposed an interim proof-of-concept trial (Phase IIb) before the initiation of a conclusive Phase III study, required for vaccine licensing. Smaller than Phase III studies, Phase IIb trials have wider confidence intervals (such as ±30%). They can be useful where vaccine candidates prove to be high in efficacy (over 60%) or low in efficacy (under 30%), as the power of the trial would show conclusively whether the vaccine was effective.

  Phase IIb trials are attractive because they offer the opportunity to get an early indication of likely vaccine success, before investing in larger and more expensive Phase III trials. Even where a Phase III study would still be required to license a vaccine, a Phase IIb study could provide interim data for basing decisions on manufacturing. This could save years in getting the vaccine to market.

  There is no consensus on the use and design of Phase IIb studies.[35] One concern is that such trials could add unduly to the length of clinical testing, although developers are discussing models where Phase IIb trials, if promising, could be expanded into a Phase III study for licensing. Another concern is that indeterminate Phase IIb results may leave vaccine candidates in limbo, with developers uncertain about whether to progress into more expensive Phase III studies. Even so, some developers are actively considering Phase IIb designs, including IAVI and HVTN.[36] Merck is due to initiate a Phase IIb trial of its AdenoVirus based vaccine in 2004, with data expected at the end of 2007.

  The public sector could support such strategies by encouraging regulatory

Vaccine developers could mitigate the risk of investment in manufacturing capacity by designing facilities that have the potential for multipurpose use

agencies and other appropriate institutions, such as the World Health Organization (WHO), to establish guidelines for such studies and to assist in interpreting trial results.

- *Reduce the cost of investment.* The public sector could subsidize manufacturing investment costs through a variety of instruments, including grants, soft loans, loan guarantees, tax credits and accelerated depreciation. To have a global impact, such subsidies should be tied to guarantees to make affordable vaccine supplies available for use by developing countries. This option is discussed further below.
- *Reduce the risk of investment.* Vaccine developers could mitigate the risk of investment in manufacturing capacity by designing facilities that have the potential for multipurpose use. Although final fitting and design specifications need to be tailored to a specific product, many of the requirements and design needs for a particular vaccine manufacturing process are generic. Where the manufacturing process required by a potential HIV vaccine can be used to manufacture other products, it may be possible to initiate construction during Phase III trials while retaining the flexibility to modify plant use until efficacy data are available.

  Such an approach would likely take longer to complete and validate a manufacturing plant, but it would be quicker than waiting for the availability of Phase III data before commencing construction. VaxGen adopted such a strategy in establishing manufacturing capacity for its AIDSVAX® candidate, which completed clinical trial trials in 2003 but failed to show efficacy (box 1).

  The public sector could subsidize vaccine developers to invest early in flexible manufacturing capacity through mechanisms similar to those just described. Subsidies could cover only the incremental costs incurred by a manufacturer in investing earlier in establishing manufacturing capacity, with no penalties if the facility is eventually used for other vaccines of lower interest to donors and to developing countries.

2. Invest early in manufacturing capacity to supply developing countries

- *Estimate developing country demand for an HIV vaccine.* An assessment of the potential demand for a vaccine is crucial to decisions on how much manufacturing capacity to invest in. But estimating global demand for a future HIV vaccine is difficult for three main reasons. First, the key characteristics of a future vaccine are not known. These include efficacy, duration of effect, delivery requirements and price. Second, more work is needed to understand the potential impact of different types of vaccines in varied epidemiological settings and to identify strategies for using vaccines effectively as part of broader

BOX 1

VaxGen—investing early

VaxGen's AIDSVAX® was the first HIV vaccine candidate to complete a Phase III efficacy trial.

In February 2002 VaxGen entered a joint venture with Celltrion, Inc. to invest $113 million in building a production facility in the Republic of Korea with a bioreactor production volume of 50,000 liters and a smaller facility in San Francisco.[a] These two plants were designed to be capable of producing 200 million doses of AIDSVAX® a year. The immunization schedule for AIDSVAX® is six doses, giving a potential production capacity of just over 33 million full immunizations a year.

Design, construction and validation of the plant were estimated to take four years, with production to start the 4th quarter of 2005.

Results from two trials of different versions of the AIDSVAX® product released in 2003, one in the United States, Canada and the Netherlands and the other in Thailand, showed no efficacy. Although investment decisions were made before the availability of efficacy data, the timings were such that, if AIDSVAX® had been successful, there would still have been considerable delay before the first supplies from the new facilities would be available.

The associated investment risks were mitigated because the technology required to produce AIDSVAX® can be fairly easily adapted to manufacture monoclonal antibodies or other vaccines (www.vaxgen.com).

a. Fink 2004.

responses to HIV and AIDS. Third, more understanding is needed of the factors that will determine uptake of a new vaccine by and within developing countries. It is also likely that different countries will adopt vaccines at different times, staggering the global uptake.

The European Commission, IAVI, the World Bank and WHO have supported initial studies on HIV vaccine demand,[37] on individual willingness to pay for vaccination[38] and on the impact of different vaccines in varied epidemiological studies.[39, 40]

Demand estimates for HIV vaccines for developing countries, backed by the kinds of data mentioned above, are an important "public good" that can stimulate vaccine developers and inform decisions on manufacturing. In addition, identifying the factors that will determine demand, such as vaccine profiles or health system capacity, can provide important information to inform vaccine design and preparation for vaccine introduction.

Estimating demand is not easy. It requires an iterative approach that improves projections as more data become available (say, on vaccine profiles). The public sector could support further work on demand estimates and impact modeling, encourage collaboration on defining realistic vaccine scenarios and assumptions and facilitate greater dissemination of results.

- *Subsidize manufacturing capacity for developing country supply.* The public sector could subsidize investment in manufacturing capacity specifically to supply demand in developing countries. Such subsidies could be grants, soft loans, loan guarantees, tax credits or accelerated depreciation. In each instance, subsidies should be contingent on producing vaccines for developing countries, perhaps including agreements on target prices for specified production volumes.

  Manufacturing partners could include large manufacturing companies in either developed or developing countries. Developing country manufacturers may offer opportunities for lower investment and operating costs. Such a partnership has recently been agreed between the Meningitis Vaccine Project and the Serum Institute of India to manufacture meningitis vaccine on a large scale for use in Africa.[41] But where novel manufacturing processes are required, developing country manufacturers are likely to require considerably more support for initial technology transfer and implementation. The public sector could put in place mechanisms or incentives to support such technology transfer, either through funds or technical support on legal and intellectual property issues.

  Governments and international financial institutions working with the private sector (such as the International Finance Corporation) would be well placed to take equity or debt positions in such manufacturing ventures. Tax credits or accelerated depreciation will depend on legislation in countries where the ventures are located.

  But unless the subsidies are very large, it is unlikely that they would ensure the supply of HIV vaccines for developing countries. Manufacturers would still seek some assurance that developing countries would be able to purchase the vaccine over a sustained period. Complementary actions are needed to develop reliable market forecasts and put in place finance strategies and purchase mechanisms.
- *Guarantee an HIV vaccine market in developing countries.* Mechanisms have been proposed to create a credible and reliable HIV vaccine market in developing countries, including advance purchase commitments and tax credits on vaccine sales to developing countries. Under the advance contracting approach, a group of funders would commit to purchasing a quantity of an HIV vaccine that meets specified criteria at a given price. If such a contract were big enough, it might provide the incentive to industry to put in place manufacturing capacity not only for rich country markets but also for the developing world.[42]

  So far, none of these advance contracting or tax relief schemes has been implemented. Some in industry express skepticism about the usefulness of these mechanisms and the degree to which public sector commitments to future vaccine purchase can be relied upon. Recently, as

Demand estimates are an important "public good" that can stimulate vaccine developers and inform decisions on manufacturing

Once the likely efficacy for a particular vaccine candidate is known, the debate over market guarantees is likely to change significantly

part of its work on pull mechanisms for new technologies that meet the health needs of the poor, the Center for Global Development has been working to devise binding contracts and contracting mechanisms that may go some way to addressing these concerns.[43] Once the likely efficacy for a particular vaccine candidate is known, perhaps from a Phase IIb trial, the debate over market guarantees is likely to change significantly—as the potential benefits of an HIV vaccine become more concrete.

Recent discussions around financial assistance for developing countries also suggest the interest of donors and developing countries in addressing access to health-related commodities (including vaccines and pharmaceuticals) in a more coordinated, predictable and sustained manner. The Global Fund to Fight AIDS, Tuberculosis and Malaria is providing a large stream of financing for antiretrovirals, antimalarials and tuberculosis drugs in a way that may improve the size and predictability of the market for these products, influencing manufacturing decisions. Similarly, the Global Alliance for Vaccines and Immunization has shown that supporting developing countries to purchase and deliver vaccines can help stimulate private manufacturers to enter the market (box 2).

Given these promising developments, as well as the current discussion about creating an International Financing Facility[44] to support the achievement of the Millennium Development Goals, it would be worth investigating and testing possible mechanisms to strengthen or guarantee the market for HIV vaccines in developing countries.[45]

3. Encourage partnerships that bring to the field the expertise to establish manufacturing capacity and launch new vaccines

- Many developers currently taking forward HIV vaccine research have no experience with large-scale vaccine manufacturing. Supporting these developers in establishing partnerships with large-scale manufacturers in developed or developing countries will ensure that manufacturing capacity for their products, if successful, will be available to supply developing country demand. Many of the proposals outlined here could assist such partnerships—such as supporting technology transfer to developing country manufacturers or providing subsidies to developed country manufacturers to increase capacity to meet developing country demand. A range of partnership models will be possible. Exploratory work is required to address a number technical issues, such as intellectual property arrangements and revenue models, that will define partnership arrangements. Equally, political commitments to support early tiered pricing for new vaccines[46] (accepting higher prices in developed countries to support lower prices in developing countries) may be important to reassuring developed country manufacturers that supporting developing country access will not undermine developed country returns.

BOX 2

Global Alliance for Vaccines and Immunization—reliable funding can make a difference

The Global Alliance for Vaccines and Immunization (GAVI) has recently shown that the availability of significant and reliable funding for developing country vaccine purchase and use can engage vaccine companies effectively. GAVI has provided support to eligible developing countries to strengthen their vaccination systems or to introduce new vaccines in their immunization programs. Vaccine companies from developed and middle-income countries have engaged with GAVI to meet this additional developing country demand. For the Hep B-DTP combination vaccine, the number of manufacturers offering the product to the United Nations Children's Fund (UNICEF), which is leading the procurement for GAVI, will rise from 1 in 2000 to 10 in 2006.[a]

a. See [http://www.vaccinealliance.org/site_repository/resources/gavi_pandc2004.pdf].

4 Conclusion

Without a fully developed manufacturing process and a plan to implement it, even the most clinically effective HIV vaccine will have no impact on the global HIV epidemic.

As described here, many developers active in the HIV vaccine field face difficulties in accessing the bioprocess and clinical materials production capacity to efficiently advance HIV vaccine development. Looking forward, there are also significant challenges to establishing the necessary large-scale manufacturing capacity that will be needed for the rapid launch of a future HIV vaccine for use by developing countries.

Existing process development barriers are already imposing extra costs on the field and slowing efforts to find an HIV vaccine. Without urgent action, current development inefficiencies could become major bottlenecks, and large-scale manufacturing challenges will not be addressed early enough to avoid significant and costly delays in launching a future vaccine.

Policy options to remove these bottlenecks and avoid the crisis have been outlined here. These options now need to be thoroughly debated and (swiftly) acted on by developing country governments, international development donors and industry.

Among the many policy options, several stand out as promising and should be more deeply explored in the coming months. They include the idea of creating a virtual bioprocess group, extending special financial assistance to vaccine developers to purchase bioprocess services, financing the expansion of bioprocess capacity and building and staffing a dedicated bioprocess facility for vaccines to address the major killers in the developing world, including HIV.

As a matter of urgency, key stakeholders in the HIV vaccine field must now work together to set priorities and develop concrete proposals to put to the G8 summit in July 2005, which will consider plans to establish and support a Global HIV Vaccine Enterprise.

Existing process development barriers are already imposing extra costs on the field and slowing efforts to find an HIV vaccine

Appendix 1: Phases in Vaccine Clinical Trials

Pre-clinical testing

Before trials in humans, candidate vaccines must first pass an extensive range of laboratory testing and animal trials to gather toxicology and other safety data and initial immunogenicity data. Satisfactory results from these studies are necessary before clinical trials can begin.

Safety and immunogenicity studies

Phase I — Controlled[a] clinical study to test the vaccine's safety in humans, including its metabolic and pharmacological actions and any side effects seen with increasing doses and to collect initial immunogenicity data.

Enroll a small number (usually 60 or fewer) healthy volunteers typically at low risk of infection.

Phase II — Controlled clinical study to identify common short-term side effects and risks associated with the vaccine and to collect expanded information on its immunogenicity, including dose ranges and scheduling (for multidose vaccines).

Enroll up to several hundred participants and include volunteers with characteristics similar to potential participants of efficacy trials.

Efficacy studies

Phase IIb — An intermediate-scale controlled study designed to show that a vaccine has an effect greater than a target threshold on the risk of infection, disease or other clinical condition at a given dose and schedule. Data from Phase IIb studies are usually not sufficient to apply for vaccine licensing but may be used to inform a go or no-go decision for the initiation of larger, more costly Phase III studies.

Enroll participants at high risk of infection.

Trial size and duration are determined by factors including expected incidence of HIV infection in the trial population, expected efficacy of the vaccine and expected duration of protection of the vaccine. Numbers of participants may reach a few thousand.

Phase IIb trials are a relatively new innovation, and there is ongoing discussion regarding their design and use.

Phase III — Large controlled study to determine the ability of a vaccine to produce a given clinical effect on the risk of a given infection, disease or other clinical condition at a given dose and schedule. These trials also gather additional information on safety. Phase III trials usually supply the efficacy data required as part of a vaccine licensing application.

Enroll participants at high risk of infection.

Trial size and duration are determined by factors including expected incidence of HIV infection in the trial population, expected efficacy of the vaccine and

expected duration of protection of the vaccine. Numbers of participants can reach many thousands.

Other studies

Bridging — Additional studies may be required to show that safety and efficacy results from Phase III studies of a particular vaccine, manufactured under a particular process in a specified facility, are reproducible in population groups not included in initial efficacy trials (such as adolescents or children).

Similarly, bridging studies will be required to demonstrate the equivalence in safety and immunogenicity of a vaccine manufactured under a different process or in a different facility to those under or in which Phase III vaccines were produced.

Scale, cohort selection and duration depend on the research question and type of study.

Phase IV — Large-scale post-marketing studies are conducted to obtain additional data on adverse events focusing primarily on events that may occur at a very low frequency.

Effectiveness — Large-scale noncontrolled studies are designed to estimate vaccine effectiveness on the risk of a given infection, disease or other clinical condition under normal field conditions.

a. A *controlled* study compares the responses of volunteers vaccinated with the test vaccine to the responses of volunteers who do not receive the test vaccine. The *control* group often receives a placebo, usually an inactive substance that does not elicit an immune response.

Notes

1. IAVI 2004a.
2. IAVI 2004b
3. IAVI 2004b.
4. Klausner and others 2003.
5. Combined Product Development and Manufacturing Working Group. The working group addressed manufacturing challenges during vaccine development and future large-scale production.
6. See http://www.g8usa.gov/d_061004d.htm.
7. Use of external contractors may be made in some circumstances.
8. IAVI 2000.
9. An *antigen* is something that stimulates an immune response in the body.
10. A number of companies do have small HIV vaccine programs. Merck, in particular, has progressed a promising candidate into Phase IIb clinical trials.
11. Mercer Consulting 2002.
12. cGMP describes regularly revised standards and procedures required of manufacturing facilities by regulatory authorities for the production of vaccines. Different requirements are specified for certain types of process or product. cGMP standards are set, revised and monitored by national regulatory authorities, such as the Food and Drug Administration (United States), although WHO provides guidelines on minimum requirements. This also means that the national regulatory authority must be competent to both set standards and evaluate ongoing implementation and compliance (see http://www.who.int/vaccines-access/quality/vaccine_quality_front.htm).
13. The U.S. Food and Drug Administration will grant a license for a vaccine based on Phase III data using clinical materials manufactured at such a pilot scale.
14. In a recent publication IAVI estimated that more than 30 HIV vaccine candidates are in clinical trials, with the majority in small Phase I studies. IAVI also notes that majority of these candidates are very similar to each other, utilising a much smaller number of vaccine approaches. See IAVI 2004a, p. 3.
15. IAVI 2004b.
16. Unpublished IAVI survey.
17. The survey identified four contract manufacturing organizations and nine biotechs that had some "live viral capabilities." Only three contract manufacturing organizations and six biotechs had formulation capabilities. Only four contract manufacturing organizations and four biotechs had asceptic filling capabilities. And only one contract manufacturing organization and no biotechs had lyophilization freeze dry capabilities.
18. Only 38% of respondents to the IAVI survey were capable of providing at least some steps in the manufacturing process for live viral vaccines, and only 30% of these had current capacity to lyophilise (freeze-dry) live virus.
19. See http://www.vrc.nih.gov/VRC/labs_gomez.htm.
20. In a recent article in the *Wall Street Journal,* the decision by St Jude's to build such capacity was explicitly linked to difficulties in accessing reliable and high quality contract services. See Begley 2004.
21. One large R&D-based vaccine company has recently shown some interest in making its bioprocess and clinical materials capacity available to HIV vaccine developers (José Esparza, personal communication, 2004).
22. See http://www.hm-treasury.gov.uk/Consultations_and_Legislation/Finance_Bill_2002/consult_finance_clause53_2002.cfm.
23. See http://www.vrc.nih.gov/VRC/labs_gomez.htm.
24. In 2003 the International Vaccine Institute moved into new headquarters in the Republic of Korea, with potential to provide public interest access to laboratory and pilot-scale manufacturing

capacity to support the development of vaccines that meet the needs of the developing countries. The institute's strategic plan for 2003–07 identifies the provision of such services as key objectives, with vaccines for Japanese encephalitis and shigella identified as priorities. Funding is still required to fully outfit laboratory and manufacturing suites, although an initial contribution for laboratory equipment has been provided by the government of the Republic of Korea.

25. It may be possible for such a facility to provide services for other priority vaccines, such as tuberculosis and malaria.

26. See http://www.vrc.nih.gov/VRC/labs_gomez.htm.

27. Unpublished report, HIV Vaccine Enterprise Working Group 2004.

28. At the upper end of this scale the facility could be used to support an initial launch of the vaccine.

29. It may be possible to adapt an existing facility to reduce startup times and costs.

30. Mercer Consulting 2002.

31. See Mercer Consulting 2002.

32. For many vaccines, researchers know what immune system response protects against the target pathogen ("the correlate of protection") and hence clinical data from Phase I and Phase II studies provide a reasonable indication of likely results in a Phase III efficacy trial.

33. As a new product, an HIV vaccine will almost certainly cost considerably more than the vaccines used widely by developing countries. In addition, an HIV vaccine will probably first be introduced in adult populations, and hence may require different delivery systems than those already established for infant and childhood vaccination.

34. Trial design depends on numerous factors including the incidence of disease in the trial population and the anticipated efficacy of the test vaccine candidate.

35. See Bass 2004.

36. HIV Vaccine Trials Network (see http://www.hvtn.org/).

37. See Esparza and others 2003.

38. See Bishai and others 2004.

39. See Stover and others 2002.

40. See Nagelkerk and De Vlas 2003.

41. See http://www.biomedcentral.com/news/20040618/03.

42. Estimates of the potential size of a market required to encourage vaccine companies to invest in the development and manufacture of an HIV vaccine have ranged from $500 million a year (see Performance and Innovation Unit 2001) up to $3 billion (Center for Global Development, see 46 below).

43. The Pull Mechanisms Working Group is based at the Center for Global Development. A report on advance contracts was released in autumn 2004. See http://www.cgdev.org.

44. The International Financing Facility is a UK government proposal to double and frontload official development assistance spending to meet the Millennium Development Goals by raising funds on the capital markets. An associated proposal is being developed to establish a facility-type mechanism to support the work of GAVI in expanding access to immunisation in developing countries. An announcement on this proposal is expected late 2004 or early 2005. See http://www.hm-treasury.gov.uk/media/1C7/AB/1C7ABBFE-BCDC-D4B3-115B84EA4BD07566.pdf.

45. See http://www.cgdev.org/.

46. Tiered pricing has long been an accepted practice for established vaccines, but usually takes a number of years to be put into place. Establishing tiered prices early in the lifecycle of new vaccines may require political commitments from developed country governments not to use low developing country prices as an index for their own price negotiations with vaccine companies.

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IAVI is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI's financial and in-kind supporters include the Bill & Melinda Gates, Rockefeller, Alfred P. Sloan and Starr foundations; the governments of Canada, Denmark, Ireland, the Netherlands, Norway, Sweden, the United Kingdom and the United States; multilateral organizations including the European Union and the World Bank; corporations such as BD (Becton, Dickinson & Co.), Continental Airlines and DHL; leading AIDS charities such as Crusaid, Deutsche AIDS Stiftung and the Until There's A Cure Foundation; and other private donors such as the Phoebe W. Haas Charitable Trust B.

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