Policy Brief

International AIDS Vaccine Initiative

Manufacturing an HIV Vaccine: Policy Issues and Options

Important progress is being made in the search for HIV vaccines. Investment in research and development (R&D) has increased considerably in recent years to over $550 million annually, with research and development now being conducted by researchers from academic, not-for-profit, public and private institutions.[i] More than 30 vaccine candidates are currently in trials, the majority in small early stage clinical trials.[ii] While this is encouraging, the ever-growing scale of the HIV epidemic requires that these efforts be accelerated.

Designing and testing a promising HIV vaccine candidate will be extremely difficult. But developing a manufacturing process for a new vaccine also presents a significant and pressing challenge.

IAVI recently conducted a survey of 274 organizations involved in vaccine development to assess the current state of manufacturing challenges and identify possible policy options to address them.[iii] This policy brief summarizes some of these challenges; for a more detailed discussion, please see the IAVI Policy Discussion Paper *Speeding the Manufacture of an HIV Vaccine: Policy Issues and Options* (see www.iavi.org).

There are two major barriers to timely and efficient manufacturing of HIV vaccines. One occurs in the product development phase: most current HIV vaccine developers work in academic institutions or small companies that lack the capacity needed to develop processes to manufacture promising vaccine candidates and produce small lots of vaccine for trials. This is discussed in section I.

The second barrier is that the high levels of scientific uncertainty and financial risk associated with developing and launching an HIV vaccine threaten to delay by many years the investments needed to make the millions of doses that will be needed for global widespread use. This is discussed in section II.

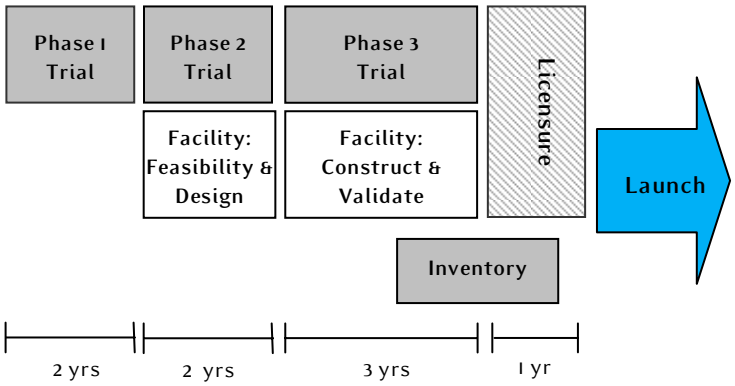
I. Product Development and the Bioprocess Challenge

As product development moves forward, a key question for vaccine developers is whether a promising vaccine concept can actually be produced effectively and affordably as a candidate vaccine. The design and implementation of a vaccine manufacturing process - known as "bioprocess development" - requires a wide range of chemical and mechanical engineering, biochemistry, and microbiology skills.

Initially, developers need to produce doses to use in Phase I and II trials that assess the candidate's safety and immunogenicity in up to a few hundred people (small-scale manufacturing). If the vaccine looks promising, then testing may progress to bigger and more expensive Phase III efficacy trials that require "pilot-scale manufacturing" to make doses for thousands of participants (see fig. 1).

To meet regulatory requirements, a developer must devise a process that can produce vaccine in the relatively small amounts needed for trials and also develop a process that can produce the amounts needed for large-scale use.[iv] But increasing the scale of a manufacturing process is not just a matter of a larger supply of ingredients

Figure 1.



and bigger equipment. Many manufacturing processes vary in non-linear ways as scale increases and as a result, technical processes that work in small volumes in a laboratory may not work at large scales.[v]

At large scales of production, small differences in yields or manufacturing efficiency can have a major impact on costs. Getting the process right for a particular vaccine is crucial to its profitability for developers and its affordability for users.

A recent IAVI survey of 274 vaccine developers and manufacturers confirms that there are serious gaps in bioprocess development to support HIV vaccine R&D. Interviews with contract manufacturing organizations (CMOs), biotechnology firms, vaccine companies, academic institutions and process development laboratories showed that:

- The large companies – Aventis Pasteur SA, Chiron Corp., GlaxoSmithKline, Merck & Co, Inc. and Wyeth-Lederle – involved in vaccine R&D have strong in-house bioprocess capabilities. Today, these companies account for 80% of global vaccine sales by value.[vi]

- Many of the other organizations currently working on HIV vaccines are academic institutions, biotechs, and non-profits that lack the in-house capacity for the full range of expertise required for bioprocess development and manufacturing.

- These small HIV vaccine developers must then contract out bioprocess development and manufacturing work to larger manufacturing organizations. Unfortunately, this often limits vaccine developers' control over the timing and quality of bioprocess development. In addition, the developers may have to work with several different contractors to procure the many services required, adding to logistical, quality and management burdens.

The delays and inefficiencies associated with this situation are already having a negative impact on HIV vaccine product development. As the number of vaccine trials is expected to increase in the next three years, things are likely to get worse.

II. Manufacturing an HIV vaccine for global use

Given the many uncertainties and risks in launching a vaccine for global use, the challenges in large-scale manufacturing are: how to determine the size of a large-scale manufacturing plant to make an HIV vaccine and how to persuade manufacturers to invest in it?

The design and construction of a large scale manufacturing plant can take 4 to 6 years and cost several hundreds of millions of dollars. Ideally, this will begin before the start of Phase III trials so that an effective vaccine can be manufactured in large amounts as soon as possible.[vii] Investing in a plant after the completion of Phase III trials will delay the vaccine by more than three years, during which time thousands of HIV infections will occur that could have been avoided.

Companies are cautious to make investments in manufacturing capacity until they are confident that the vaccine candidate will be granted a license and that there will be a sufficiently large and profitable market. Unfortunately, on a global scale, neither of these conditions hold true for HIV vaccines today.

A facility must be scaled properly to meet anticipated demand in the target markets. If a plant is too big, costs will be unnecessarily high; if a plant is too small, vaccine shortages will occur. Correcting a failure to build adequate manufacturing capacity can take years (see box 1).

To recoup investments quickly, companies launch new vaccines in predictable high-value markets in the developed countries.[viii] However, since 95% of HIV infections take place in developing countries, it is imperative that manufacturing capacity should be built to meet global demand, not just the demand of the developed world. The likely demand from Africa, Asia, Latin America, and other developing regions needs to be estimated now to plan for the future.

Given that much of the global demand for an HIV vaccine will come from poor countries that are least able to pay, the donor community, governments and NGOs must work now to devise a mechanism to ensure that there will be adequate purchasing power for an HIV vaccine. To date, no firm financing commitments have been made to guarantee a viable

HIV vaccine market and reduce the financial risks to manufacturers, although the United Kingdom and others have started to talk about "advance purchase commitments."[ix]

III. Public Policy Options

A number of policy options may encourage early investment in bioprocess development and large-scale manufacturing for an HIV vaccine.

a. Product development

- *Provide support for improved management of existing bioprocess development capacity.* Donors could support the creation of a virtual or real team of bioprocess development experts that would offer services and facilities to participating HIV vaccine developers.

- *Increase public financing to small HIV vaccine developers to purchase product development service from third parties.* Finance could be provided through a variety of mechanisms, including grants, tax credits, and soft loans, depending on characteristics and needs of the recipient.

- *Increase the supply of bioprocess development capacity by directly financing bioprocess organizations.* Donors could add capacity at public sector institutions, such as the US National Institutes of Health. Alternatively, grants, soft loans and tax credits could be provided to biotechs, CMOs and developing country manufacturers to invest in bioprocess development suited to the needs of HIV vaccine developers.

- *Invest in a "public interest" bioprocess facility for HIV vaccines.* A dedicated facility could pull together the expertise and capacity needed, mimicking the approach of large R&D-based vaccine manufacturers. This option would be more costly than those above but may have greater potential to expand global bioprocess development capacity over the long term.[x]

b. Large-scale manufacturing

Although the public sector has a clear interest in the swift global availability of a safe, effective HIV vaccine, currently the private sector product developer bears all the financial risk associated with manufacturing. Policies are needed to stimulate greater involvement by large manufacturers and to share risk between the public and private sectors.

Box 1
VaxGen—a case study

The experience of VaxGen, a California biotech whose AIDSVAX® was the first HIV vaccine candidate to complete a Phase 3 efficacy trial, illustrates the risks of vaccine manufacturing. In early 2002, VaxGen made the decision to invest $113 million to build two plants to produce AIDSVAX®, with construction to take four years.

Unfortunately, results from trials released in 2003 showed no efficacy. Although investment decisions were made before the availability of efficacy data, the timing was such that if AIDSVAX® had been successful, there would still have been a delay of at least a couple of years before the first supplies were available. Nor would these supplies have been sufficient: the plants would have had potential production capacity of just over 33 million full immunizations a year, far short of likely global demand for an HIV vaccine.

However, in the end, the disappointing trial results led to the opposite problem: a plant with no HIV vaccine to produce. Fortunately for the company, the associated investment risks were mitigated because the technology required to produce AIDSVAX® could be adapted to manufacture monoclonal antibodies and other vaccines (see www.vaxgen.com).

- *Create incentives to promote early investment in manufacturing capacity, particularly for developing countries.* Grants, soft loans, loan guarantees, tax credits and accelerated depreciation could be provided to potential manufacturers, in exchange for guarantees that the vaccine would be made available at affordable prices in developing countries. Incentives could be used to support the transfer of technology from large pharmaceutical companies to interested developing country manufacturers.

- *Provide guarantees of a market for HIV vaccines in developing countries.* Tax credits on vaccine sales to poor countries could lower the price of an HIV vaccine and increase demand. Or advance purchase

commitments could be used to reassure manufacturers that there is a viable market for the vaccine in poor countries. Under advance purchase commitments, funders would commit to pay for a given quantity of vaccine that meets specified criteria at a given price, providing industry with incentives to scale manufacturing capacity to meet both developed and developing country demand. [xi]

IV. Moving Forward

IAVI believes that both the bioprocess and large scale manufacturing challenges facing HIV vaccines now need to be urgently addressed. For bioprocess development, a way must be found to help the small vaccine developers access high quality bioprocess engineering services in a timely manner. For manufacturing, a detailed assessment of the demand for an HIV vaccine in developing countries and the establishment of advance purchase commitments are top priorities.

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 accelerate HIV vaccine development by facilitating better collaboration, mobilizing increased resources, and addressing strategic challenges – including manufacturing.[xii] Group of Eight leaders endorsed the Enterprise, with specific mention of manufacturing, at their 2004 summit.

To move forward, these manufacturing policy options need to be thoroughly debated by key stakeholders, including developing country governments, international development donors, and product developers and the results fed into policy-making forums, including the 2005 G8 summit to be hosted by the UK. An action program should be formulated and endorsed during 2005, so that it can be implemented thereafter.

Notes and References

[i] International AIDS Vaccine Initiative (IAVI). 2003. *Global Investment and Expenditures on Preventive HIV Vaccines: Methods and Results for 2002*. New York.
[ii] IAVI. 2004. *Scientific Blueprint 2004: Accelerating Global Efforts in AIDS Vaccine Research and Development*. New York.
[iii] IAVI. 2004. Unpublished IAVI survey. New York.
[iv] To gain regulatory approval, bioprocess development also must provide analytical tools to demonstrate that the same vaccine, at the same quality level, is being tested in all trials.
[v] To gain regulatory approval, bioprocess development also must provide analytical tools to demonstrate that the same vaccine, at the same quality level, is being tested in all trials.
[vi] Mercer Consulting. 2002. "Lessons Learned: New Procurement Strategies for Vaccines." New York.
[vii] For many vaccines, researchers know what immune system responses protect against the target pathogen. Thus, clinical data from Phase I and Phase II studies provide a reasonable indication of likely results in a Phase III efficacy trial.
[viii] Although developed countries account for only 12% of worldwide vaccine sales by volume, they make up 82% of the global vaccine market by revenue. Mercer Consulting. 2002.
[ix] In a December 2004 speech to the Council of Foreign Relations, UK Chancellor of the Exchequer Gordon Brown stated the UK government's commitment to the International Financing Facility, which would leverage donor commitments to raise funds for international development efforts, including pledges to purchase large amounts of vaccines for developing countries (see www.cfr.org).
[x] Cost estimates for designing and building such a facility range from $60 million to $300 million, depending on the range of process technologies implemented and the scale of production possible. HIV Vaccine Enterprise Working Group. 2004.
[xi] The Center for Global Development in Washington D.C. examines these issues. See the working draft of their brief *Making Markets for Vaccines*, www.cgdev.org.
[xii] The Global HIV Vaccine Enterprise established a Product Development and Manufacturing Working Group to address manufacturing issues during vaccine development and future large-scale production.

About IAVI: IAVI (www.iavi.org) IAVI (www.iavi.org) 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.