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Vaccines MANUFACTURING

## An Alternative to the Scale-up and Distribution of Pandemic Influenza Vaccine

With baculovirus-based production in disposable equipment, vaccine can be available 10 to 12 weeks after an outbreak.

James M. Robinson

### Abstract

*An influenza pandemic is a global health risk and many solutions are being developed to attempt to address this serious threat. Vaccination is thought to be a preferred solution, although access to a timely and sufficient supply of vaccine against a new emerging pandemic strain is inadequate in every country around the world. A new approach makes it possible to provide vaccine within 10 to 12 weeks of identification of a new viral strain, with an exact match to the wild-type influenza strain, by using disposables-based manufacturing facilities that can be built more quickly and cheaply than traditional vaccines plants.*

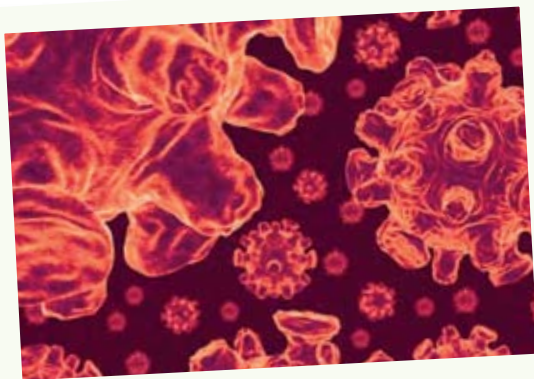
### The Current State of Preparedness

The threat of an influenza pandemic is well recognized. Many thought leaders in the field believe it is a matter of when, not if, a pandemic event will occur. The threat has triggered emergency preparedness efforts in many developed countries and the result has been the purchase of multiple medical countermeasures including stockpiles of medical supplies (e.g., masks, gloves), antiviral drugs (e.g., Tamiflu), and the development and stockpiling of vaccines against multiple prepandemic strains of the H5N1

influenza virus (e.g., A/Vietnam, A/Indonesia, A/Anhui). Because the total supply and cross-reactivity of these stockpiled vaccines is insufficient for mass immunization, adjuvants are also stockpiled, to stretch the available antigen supply and to improve the cross-reactivity of the vaccines we can make today.

As a result of this government-sponsored procurement and development of these medical countermeasures, there is clearly an improved state of preparedness today in some specific countries, particularly the US. However, vulnerabilities remain even in the best-prepared coun-

**Virus-like particles (VLPs) mimic a natural virus in size, structure and surface proteins, but do not have the nuclear material necessary for infection. They trigger an immune response as if a natural infection takes place.**



Novavax, Inc.

tries, and the majority of the global population remains unprotected. No country has a supply of vaccine for a novel influenza strain (e.g., H2, H7, H9), as the focus of development efforts to date has been on various strains of H5N1. No country has a sufficient supply of vaccine without adjuvants, and the adjuvants have not been proven safe in large-scale clinical studies. Most countries do not have influenza manufacturing capabilities within their national borders, and because borders will close on the declaration of a pandemic to control the spread of disease, vaccine distribution will also be hindered. In addition, it will be politically difficult to ship precious vaccine out of a country until all citizens are protected. In the end, most countries would be left without a supply of pandemic vaccine.

### The Challenges of Ensuring Sufficient Supply

Today, the vast majority of influenza vaccines are made by growing the target influenza virus in fertile chicken eggs. The eggs are infected with the virus, the virus is allowed to grow for several days, and then the virus is removed from the egg, purified, inactivated, and treated with detergent to remove most egg and influenza proteins other than the hemagglutinin (HA) protein. (Antibody to HA from immunization will neutralize a similar virus on infection and is thereby correlated with protection from disease risk).

Newer methods are being developed to replace the chicken egg with a cell line developed from various mammalian species, although the purification and inactivation are managed in a similar manner.

The cost of developing new vaccine production capacity by traditional means is prohibitively expensive. New facilities in the US have been reported to cost \$150 million for large-scale egg-based (100 million doses/season) and to \$600 million for mammalian cell-based (50 million doses/season) facilities. These high costs have resulted in large centralized facilities in developed countries where the market value is high, with excess supply being exported to other markets.

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## The cost of developing new vaccine production capacity by traditional means is prohibitively expensive.

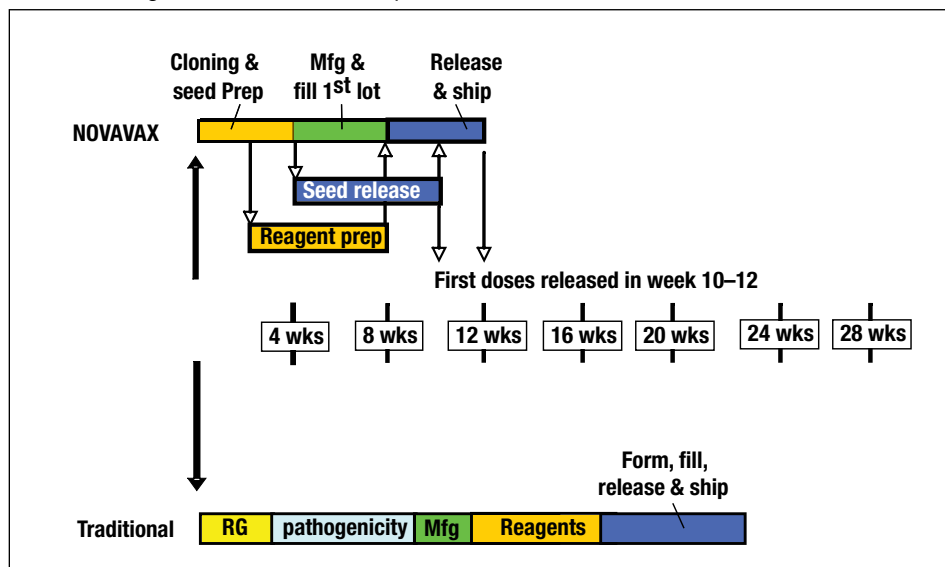
In addition, the capacity needed for a rapid and complete pandemic response is far greater than the seasonal influenza vaccine demand. Building capacity for the pandemic need would result in overcapacity for seasonal needs. Such new capacity would be severely under-utilized, or the market for seasonal vaccine would be overserved, lowering prices and margins and hence diminishing the financial returns required to build and maintain the operational infrastructure for manufacturing under current good manufacturing practices (CGMPs). This may already be the case in the US, where new facility projects (e.g., Solvay's cell culture plant) are being shelved because of poor economics, even with government cost-sharing for new facilities.

Many governments are aware of these problems and the need to create supply within their borders. However, the initial high capital requirements for traditional approaches have left them with a list of expensive alternatives that are difficult to justify given the uncertainty of the pandemic need. Likewise, a facility built to react to a pandemic event would only be effective if it were in a constant state of readiness for production, because equipment needs to be exercised and maintained, and people must be trained. This state of readiness can be accomplished only by making other products in the facility and then switching to pandemic flu vaccine production when needed. The best fit would be seasonal influenza production for the local market, but this has important implications for global influenza vaccine oversupply, competition, and the utilization of capital, as the facility would likely not be well suited for other vaccines made by traditional means.

### An Alternative Approach: Baculovirus Production in Disposable Equipment

Novavax, Inc. (Rockville, MD), is developing a novel, recombinant vaccine using cell culture to rapidly produce three proteins specific to an emerging influenza strain that self-assemble into an enveloped, non-infectious particle (virus-like particle or VLP) resembling the influenza virus. The approach provides vaccine within 10 to 12 weeks of identification of the new strain and provides an exact match to the wild-type influenza strain. Yields are significantly higher than egg and mammalian cell culture production. The high yields and use of a nonpathogenic baculovirus allows production in disposable manufactur-

**Figure 1.** The insect-cell based vaccine can be ready in 10–12 weeks, compared to 24 for a traditional method. Part of the time savings is achieved by preparing the reagents for lot-release testing while the vaccine is in production.



ing equipment. The use of disposables radically lowers facility costs, making the solution affordable to many governments. These advantages are explained below.

The time required to manufacture this insect-cell based vaccine is 10–12 weeks, as shown in Figure 1. This time includes four weeks to make recombinant baculovirus production seed stock from the native influenza virus DNA or from the DNA sequence identified by the relevant health agencies, such as the Centers for Disease Control or the World Health Organization. These seed stocks are used to make manufacturing lots starting in week 5. In parallel, recombinant hemagglutinin (HA), neuraminidase (NA), and matrix (M1) protein are made for the generation of reagents needed for lot-release testing. During weeks 8 to 10, vaccine lots, which have been in production since week 5, are formulated, filled, and packaged for distribution, with release expected in weeks 10 to 12. This is approximately the same time that the first pandemic wave of disease will peak, so having vaccine available this quickly offers the potential to halt the pandemic in its tracks. Traditional manufacturing processes, in contrast, require preparation of a nonpathogenic virus (because an avian virus would kill the fertile egg used in production), and then production of materials used to make reagents. Only when these reagents are available can vaccine be released. The traditional process in this case takes at least 20 to 24 weeks, which means that vaccine is not available until the second wave of pandemic disease, after much of the damage has been done.

The insect-cell production system also has a very high productivity compared to traditional

approaches (Figure 2). Yields in the production of HA are 7–10 times higher (in grams of protein per volume of production lot) than with traditional methods. These high yields make it possible to use small disposable reactors (1,000–2,000 L) instead of 20,000-L reactors needed for mammalian cell culture production. The system developed for making Phase 1 and Phase 2 clinical lots uses 200-L Wave reactors (GE Healthcare, Uppsala, Sweden) for the production of VLPs, followed by a series of purification steps that are also executed in disposable

### The high yields in the insect-cell platform make it possible to use small (1,000–2,000 L) disposable reactors.

equipment. The current high yields are expected to increase as high-performance disposable stirred reactors (Xcellerex Inc., Waltham, MA) are used to scale up the process to 1,000 L for commercial production. Higher gas transfer rates are expected to support higher insect cell culture densities, thus providing higher volumetric productivity. Further, clinical testing to date has shown that much smaller doses of the VLP vaccine are needed to match the effectiveness of licensed pandemic vaccines (without the use of adjuvants). This means that the yield advantage is further magnified to >40-fold higher productivity in terms of doses of vaccine per liter of cell culture.

### Lowering Manufacturing Costs

Novavax contracted Jacobs Engineering (Conshohocken, PA) to provide a conceptual design and cost estimate of a facility for making influenza vaccine using the VLP manufacturing technology in disposables. The plant, which would be capable

## The commercial-scale facility will use manufacturing systems identical to those used in the pilot plant, so no scale-up is required.

of producing 75 million doses per season, would be one-third the size of a facility of similar capacity designed for vaccine production in eggs or mammalian cell culture (assuming the same dose).

The cost of the new facility is estimated at \$40 million, one-twelfth the cost of the mammalian cell culture facility at 50 million doses per season. The savings result in part from the higher yield, but mainly from the use of disposable manufacturing systems. Instead of large, fixed stainless-steel equipment, connected by a maze of piping and process controls, with automated cleaning and sterilization systems, the disposable approach uses free-standing skids with removable liners, flexible tubing, and disposable filters and chromatography columns. The result is the avoidance of the ever increasing cost of stainless steel, as well as the need for the clean-in-place and sterilize-in-place equipment, parts washers, and clean steam generators required for traditional processes. Further, other facility systems, like contaminated waste collection and kill systems and water-for-injection (WFI) systems are small, because all product contact parts arrive presterilized and are discarded after one use without cleaning. (In a traditional manufacturing process using stainless-steel equipment, cleaning processes contribute the vast majority of the volumes of purified water). This disposables-based approach also requires much less labor. An apparent waste issue of the disposable approach is the volume of plastics that are discarded. However, these high-energy

plastic side streams can be incinerated with the cogeneration of power to minimize their environmental impact.

### Scale-Up Speed

The smaller, less-complicated facility also can be built, commissioned, qualified, and validated much more quickly. The sequential validation of multiple water and steam systems is avoided; as well as the cleaning and sterilization validation required to begin process execution. The final Novavax facility will use manufacturing systems identical to those used in the pilot plant, so no scale-up is required, only the confirming validation runs duplicating what has already been intensely validated during the process development. The result is project execution in about two years, compared to four to six years for a traditional facility. The shorter time supports earlier availability of product for a pandemic, as well as faster recovery of the investment permitted by the shorter and less expensive project.

### Comparison of Variable and Fixed Costs

From a cost of goods sold (COGS) perspective, the cost of insect-cell based VLP vaccine is equivalent to the egg-based influenza manufacturing process based on current yields (Figure 3). However, the mix of costs is quite different. Although eggs are a relatively expensive raw material, the remaining raw material costs of egg-based flu vaccines are low. By comparison, the disposable equipment in the Novavax process (e.g., reactor bags, chromatography resin/columns) are more costly. The 7- to 10-fold higher yields of the No-

vavax system make the per-dose costs reasonable, however, and additional yield gains should provide a COGS advantage for insect-cell based production. One key advantage of the disposable approach is the low labor requirements, because equipment is not cleaned and because the early steps of the egg-based system (i.e., the handling of the eggs) is very labor intensive. Thus, these factors cancel each other out, making the overall variable costs of the two approaches very similar (per gram of HA).

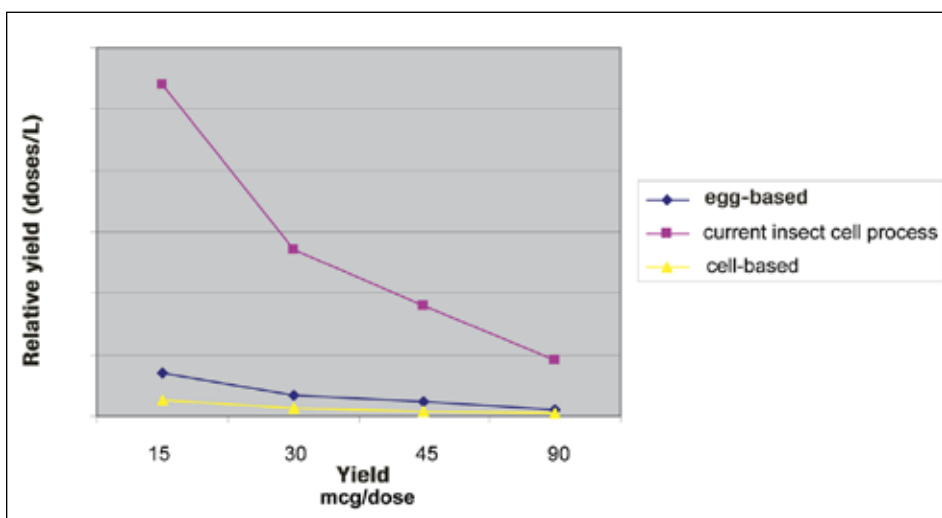
On the fixed cost side, however, the disposable approach has a significant advantage. Lower capital costs mean less depreciation as a fixed cost. Likewise, the lower energy consumption of disposables (no cleaning/sterilization, lower water use) also reduces fixed costs in the facility. The more important impli-

**This insect-cell based process can be adapted easily to make other VLP vaccines. A change in clone is all that is required.**

cation of low fixed costs, however, is that high facility capacities are not needed to reduce the unit cost impact of the fixed costs. That is, you lose the need for economies of scale and hence you can effectively build a smaller plant, suited for the local population, rather than a large plant to cover many regions.

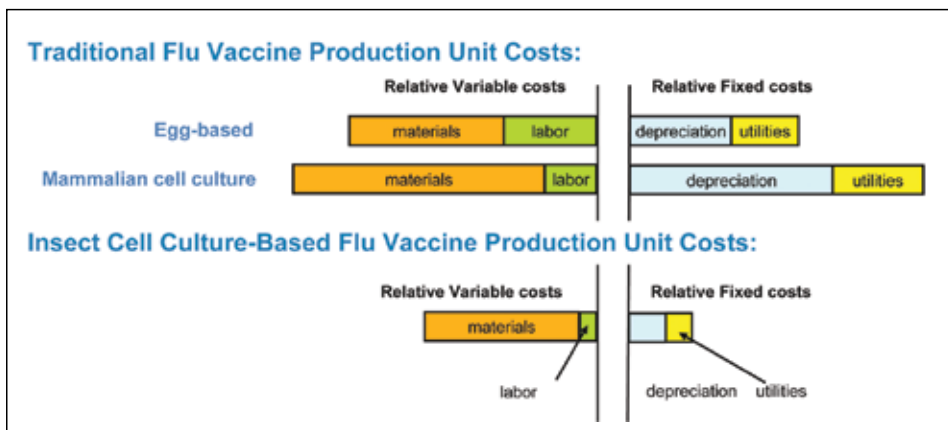
### Proof of Concept

To demonstrate this concept, Novavax has built a pilot plant and commercial launch facility in Rockville, MD, with a fully disposable process capability. The facility houses a single 1,000-L Xcellerex Bioreactor for VLP production, supported by two Wave bioreactors and a 200-L Xcellerex bioreactor for seed preparation. At current yields, the existing process equipment can produce up to 30 million doses of H5N1 vaccine in six months (at 15 mcg/dose). We expect yield to increase such that the facility can support up to 80 million doses in six months, once the new bioreactor conditions are optimized. The facility was built for less than \$6 million. The facility is a prototype of what we could place “in-border” to support a government’s desire to secure its supply of pandemic vaccine. The overall cost for a facility would be higher than the quoted price, as the Rockville facility does not include formulation, filling, packaging, or media and buffer preparation, which will be contracted out. The cost also does not include quality control or quality assurance space. It still represents a good order-of-magnitude savings over what would be possible with traditional flu vaccine manufactur-



**Figure 2.** Relative yield from traditional vaccine production compared to baculovirus production of a virus-like particle (VLP) based vaccine. Because the VLP vaccine is effective at a much lower dose, the effective yield of the baculovirus production system is 42 times higher.

**Figure 3.** Comparison of the relative variable and fixed costs of traditional vaccine production facilities and insect cell culture–based production.



ing approaches and provides countries with a proof of concept for the approach. The construction and qualification was completed in 120 days, which shows the time savings of the disposable approach as well. The facility became fully operational at the end of 2008.

**Customizing Vaccine Supply by Region**

In addition to securing pandemic influenza vaccine supply, this technology approach offers other advantages. First, this technology makes it possible to customize vaccine for a given region. Some regions do not get great benefit from the recommended vaccine formulation. When influenza strains emerge in Southeast Asia, they mutate as they migrate across Asia into Europe and North America, then Africa and South America. The strains recommended for Europe and North America have already passed through Southeast Asia and a different vaccine formula would be advantageous in that region.

Further, additional antigens may be warranted in a region, because multiple B strains can circulate and choosing just one for the seasonal formula has the potential to reduce a vaccine’s effectiveness if the alternate strain were to become prominent. Therefore, having local capacity gives governments an opportunity to add an ad-

ditional strain (even a pre-pandemic avian strain) to the formula to add value to the seasonal vaccination program.

Next, there are sometimes ‘late-breaking’ strains of influenza that are antigenically variant from the seasonal formula. The speed and yield of the process in insect cells affords the local government the opportunity to make an additional vaccine in a timely manner to address this risk as needed.

**A Flexible Facility**

Finally, the process that Novavax has developed for influenza vaccine production is also effective at making other VLP vaccines. The company is developing other VLP vaccine candidates in collaboration with the US National Institute of Health (NIH) that use the same process as influenza manufacturing in insect cells. A change of the clone alone is required to make alternate VLPs. As these and other similar vaccines are developed and approved, pandemic facilities can be used to manufacture these products for local markets. This increases facility utilization and provides a “warm base” operation so the facility is always ready to switch to pandemic influenza vaccine manufacturing mode.

Because Novavax is a 100-person vaccine de-

The speed of this process gives local governments the opportunity to make an additional vaccine for local and late-breaking strains.

velopment company, the ability of this company alone to help the world create a better solution to pandemic influenza is limited. In December 2007, Novavax signed a collaboration with GE Healthcare to expand its ability to provide a pandemic solution to governments around the world. GE is a large company with a history of innovation and a track record for delivering large projects, and the company already serves many governments by constructing hospitals and utility plants. GE will provide the facility engineering, project management, and government access to support the Novavax technology application in delivering in-border or regional vaccine manufacturing capabilities to those that have recognized the need to create this valuable resource.

**Summary**

An influenza pandemic is a recognized global health risk and many solutions are being developed to attempt to address this serious threat. To date, most solutions fall short of providing an effective response to protect the global population. Vaccination is thought to be a preferred solution, although access to a timely and sufficient supply of vaccine against a new emerging pandemic strain is inadequate in every country around the world. Novavax, Inc., teamed with GE Healthcare, can offer a solution that answers the call for a fast vaccine response to a novel influenza vaccine strain using an affordable technology for many developed and emerging countries. With the help of government and nongovernmental organizations, the technology can also be available to developing countries. This approach is economically rational and its implementation may actually be capable of halting a pandemic in the countries where it is most likely to start, where those populations have no defense today. ★

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