Cell-based flu vaccines ready for US prime time

Modernized flu vaccine production systems are approaching Food and Drug Administration (FDA) submission, promising improved control over the economic and health impacts of annual cycles and pandemic outbreaks.

Andy Extance

Egg-based flu vaccines have long ruled the US marketplace, but alternatives are finally catching up. Mammalian cell-based production systems — many of which cultivate the flu virus in kidney cell lines rather than in eggs — are as safe and effective as established systems, show the first published pivotal trial data from two leading candidates: Baxter's Preflucel and Novartis's Optaflu. Although both of these vaccines are already approved in the European Union, these results are set to provide the additional efficacy and lot-to-lot consistency data that are required for US regulatory submissions.

Baxter's Phase III trial of its inactivated Vero cell-derived flu vaccine Preflucel provided 78.5% protective efficacy against matched flu strains, the company reported in the *Lancet*. "The FDA requirements for licensure of flu vaccines in this kind of study is that the lower 95% confidence interval must be at least 40%," explains Noel Barrett, the Vice President of Research and Development, Vaccines at Baxter. "We very comfortably achieved the requirement." Last year, Novartis reported in *Clinical Infectious Diseases* that its MDCK cell-derived Optaflu vaccine was at least as effective as an egg-based comparator — 83.8% and 78.4% efficacy, respectively — and also exceeded regulatory efficacy and immunogenicity requirements.

If all goes to plan, mammalian cell-based flu vaccines could gain US approval by next year. Novartis aims to file Optaflu with the FDA by the end of 2011. Baxter is still finalizing its US approval timeline.

IMAGE SOURCE

Director of the US National Institute of Allergy and Infectious Disease Anthony Fauci welcomes the progress these studies mark towards getting these flu vaccines onto the US market. "The egg system is cumbersome, requiring multiple steps, each of which could run afoul of technical difficulties," he says. Pandemic flu strains can be particularly taxing for the outdated production system — when the Fujian H3N2 flu strain emerged in 2003–2004, for instance, matched vaccines could not be created in eggs fast enough.

Mammalian cell-based systems, by contrast, side step the logistical challenges of working with eggs. They also allow better batch control and more flexibility in terms of the speed and volume of production. "We can deliver a vaccine 8 weeks ahead of the egg manufacturers," Barrett says.

Money motivates

Vaccines for other infectious diseases, such as rotavirus and polio, have been produced using cell systems for decades. Yet flu vaccine producers have been reluctant to convert. "Influenza vaccinology got stuck in an antiquated technology and is just now making the leap into a more modern approach," explains Fauci.

The delayed transition from eggs in the United States is due to close regulation and low prices and profit margins of flu vaccines, says Russell Thirsk, the site head of Novartis Vaccines and Diagnostics' Holly Springs, North Carolina, USA, manufacturing facility. "People can make money with traditional egg-based systems, whereas cell-based systems don't save them a huge amount of manufacturing costs and they're not necessarily much more efficacious."

With H5N1 and H1N1 flu pandemic strains emerging in recent years, however, concerns about production speed and volume have increased. Consequently the US government has provided financial motivation to push manufacturers to change their approaches. "There have been investments of over a billion dollars to help companies make the transition," says Fauci.

Some of this funding has also gone towards the development of products that do not require production of the whole flu virus. These include recombinant proteins and virus-like particles that can be produced in cell culture. Among the leads in these products are Protein Sciences Corporation's FluBlok, a vaccine comprising recombinant haemagglutinin antigens that is produced in a moth cell line. In 2009, the FDA declined approval for FluBlok and requested additional safety studies. It has been resubmitted and is currently under review.

Other alternatives include viral vectors, in which a flu protein is expressed on the surface of a 'carrier' virus. DNA vaccines — in which viral genes are introduced into the human host via DNA plasmids, transcribed and then translated into pathogenic antigens — are also under development.

Fauci argues that these recombinant technologies must also reach the market for flu vaccine production to be sufficiently responsive. "I don't think that cell-based growing of flu virus for a vaccine is the end game," he says.

The benefits of the recombinant systems include added speed even above cell-based systems, says Rahul Singhvi, Chief Executive Officer of Novavax. "We can simply use the genetic sequence information, which can be e-mailed to us as soon as it's determined, to synthetically construct the genes, and then we're on our way," he says.

Novavax recently reported positive Phase II results of its recombinant virus-like particle product — a protein shell decorated with haemagglutinin and neuraminidase. The results showed that whereas traditional flu vaccines contain 15 μg of haemagglutinin per strain, Novavax's vaccine provided acceptable immune response with just 5 μg. "Our approach has the potential of making more potent vaccines," says Singhvi. Having received a US government contract from the Biomedical Advanced Research and Development Authority in February this year for up to US$180 million, the company plans to push its vaccine into Phase III trials soon.

Although such products do pose a direct threat to the commercial success of cell-cultured whole virus vaccines, Thirsk considers it to be remote. "The big constraint around these vaccines is the time it takes to build the manufacturing capability," he says. Singhvi highlights, however, that investing in more than one technology improves the US government's chances of getting improved flu vaccines. "It's a portfolio approach," he says. "They're placing their bets and then hoping that both cell culture and recombinant cell culture technologies work."

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