Vaccine makers' immunity questioned in court

The US Supreme Court has begun considering how much liability vaccine makers have if the side effects of their products are believed to have injured or killed someone. The case was brought against Wyeth (now merged with Pfizer of New York) by parents of Hannah Bruesewitz, who in 1992 began suffering seizures and developmental problems after being given the combined *Corynebacterium diphtheriae* toxoid/*Clostridium tetani* toxoid/polio (DTP) vaccine against diphtheria, tetanus and pertussis (whooping cough). A few years later, DTP was removed from the market and replaced by a vaccine with fewer side effects. The Bruesewitzes believed their daughter's injuries were avoidable because Wyeth should have put a product with fewer side effects on the market earlier.

What is most notable about the *Bruesewitz v. Wyeth* case, which was argued on October 12 in Washington, DC, is that many in the US drug industry had believed that the issue had been completely resolved with the adoption in 1986 of the National Childhood Vaccine Injury Act. The act set up a Vaccine Court to adjudicate claims of injury on a no-fault basis and pay successful claimants with money generated from a tax on vaccines. The Vaccine Act was put into effect because of a fear at the time that lawsuits claiming 'design defects' would force companies to stop making vaccines. Accordingly, the act says suits cannot be filed against manufacturers "if the injury or death resulted from side effects that were unavoidable, even though the vaccine was properly prepared and was accompanied by proper directions and warnings."

There is a back door to the law that allows families to go to a federal court if they lose in Vaccine Court or they don't like the amount of its judgment. However, those suits are governed by the Vaccine Act, too.

But neither the Vaccine Court nor a lower US federal court accepted the Bruesewitzes' argument that their daughter's injuries could have been avoided by the manufacturer. However, the justices found the wording in the Act, and especially its use of the word "unavoidable" quite confused. Justice Stephen Breyer remarked "it's pretty hard to say the word unavoidable means avoidable." A final judgment is expected in early spring of 2011.

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Varmus, then at the Memorial Sloan-Kettering Cancer Center, also estimates the time it would take before these changes could be instituted.

From rapid sterility testing, to accelerated virus seed production and improved adjuvants, each advance could slice several weeks off the time for the first dose to reach the market. The PCAST committee members believed these changes individually could be put in place within 1 to 3 years. To change egg-based vaccine production systems for alternative cell or recombinant DNA platforms would require longer—up to a decade—to reach market penetration.

BARDA's R&D money will help push a broad swath of potentially game-changing new technologies, but deputy assistant secretary of BARDA, Robin Robinson, admits that it doesn't cover the gamut of vaccine innovations in development. In particular, Robinson points to efforts to grow vaccines in plants and insect cells. Some of these projects are being funded by other US government agencies, most notably the Defense Advanced Research Project Agency, which is supporting four tobacco-based vaccine production platforms.

In plants, the process is quicker than in eggs. Andy Sheldon, president and CEO of Medicago of Quebec City, Canada, says "it takes five weeks to grow the tobacco, the plants start expressing the protein in five days, and then it takes two days to purify the VLPs [virus-like particles]." He compares this to the six months egg-based vaccine production takes. Medicago is entering phase 2 clinical trials with its plant-derived flu vaccine.

Plant-based production is cheaper too. The manufacturing facilities Medicago plans for Raleigh, North Carolina, will cost $25 million to build, a far smaller investment than the $250 million required for an egg-based production plant and the $1 billion that Novartis recently spent on a new Holly Springs, North Carolina facility. If approval is granted, it will become the first facility in the United States licensed to use mammalian cells to produce flu vaccines and is expected to be operational in 2013.

A seasonal influenza vaccine, FluBlok, produced in insect cell culture, could be on the market next year. Protein Sciences of Meriden, Connecticut, received a BARDA contract in 2009 to use cells from fall armyworm (*Spodoptera frugiperda*) with a baculovirus system to generate influenza VLPs. Protein Science's president and CEO, Manon Cox, says it takes about two months from virus discovery to vaccine production using insect cells for production. It is also cheaper than egg-based vaccine manufacturing. "Licensed vaccines cost approximately $1 a dose to make the active ingredients. Our estimates are that we can make three times more product for that price," claims Cox. Protein Sciences is waiting for US Food and Drug Administration approval of FluBlok.

Pfenex, too, says its technology is nearing the market. Last year, the Defense Threat Reduction Agency provided the company with a DNA sequence of an unknown antigen and challenged them to develop both a production strain and a high-speed, high-quality, low-cost, antigen-production process. In conjunction with partner organizations, Pfenex used its screening technology to do this within 42 days. And there were cost savings. "If you scaled up to production levels, the antigen can be produced for ~50 cents per dose," says Patrick Lucy, Pfenex's vice president of business development.

But the issue that looms largest in the push to modernize and speed up vaccine development relates to the business end of things. How are these innovative technologies going to fit into an existing vaccine marketplace that—influenza pandemics and potential terrorist bio-attacks aside—generally satisfies the world's vaccine needs?

For example, the PCAST report pointed out that although the Novartis cell culture facility was likely to generate annual profits of $30 million, it "would take over 30 years to recover the [$1 billion] investment in nominal dollars (leaving aside the need for a return on investment)."

Protein Science's Cox argues this naturally leads vaccine manufacturers, using egg-based technologies, to resist any change. "They are not going to easily let that [advantage] be taken away by a new technology in which their learning curve is going to be as steep as anybody's else's," she says. Rafick-Pierre Sékaly, co-director and scientific director of the Vaccine and Gene Therapy Institute of Port St. Lucie, Florida, concurs. "The president and the committee can make all the recommendations they want but if the big vaccine makers say it is too costly or there is too much R&D, then changes are going to be treated not as a solution but as an added burden."

On this point, BARDA's Robinson says, "we understand, and that is why we are pushing things that will definitely benefit all vaccines, including eggs." Indeed, in October BARDA awarded Sanofi Pasteur of Lyon, France, a 3-year, $57 million contract to make more fertilized eggs available for vaccine production on a year-round basis.

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