

Vaccine Technology Outpacing Ability To Predict Adverse Events, FDAer Says

Advances in vaccine technology may be outpacing researchers' ability to predict potential vaccine-related adverse events, Center for Biologics Evaluation & Research Viral Products Division Director Peter Patriarca, MD, said at a recent forum on immunization issues.

While several of the new approaches to vaccine development are considered "very exciting" by FDA, Patriarca said, that excitement is tempered by the "important new challenges in terms of vaccine safety" that these advances pose.

* "One of the important things is that the technology used to make these vaccines actually exceeds the science and technology to understand how these vaccines work and to predict how they will work," the CBER official said. "So this has the potential for ending up in a situation which I call a 'black box' vaccine."

* One example of a "black box" vaccine emerged with the recent withdrawal of Wyeth-Lederle's rotavirus vaccine *RotaShield* after the product was linked to several cases of intussusception. Because of uncertain host-range restrictions associated with RotaShield, FDA reviewers could not predict how the vaccine would behave when administered to large numbers of children, Patriarca explained.

Patriarca also noted that problems can arise when a vaccine's antigenic determinants are unknown, where neutralizing epitopes are variable or where the virulence genes are not established.

Other challenges in vaccine development include cases where preclinical studies can prove prohibitively expensive, as with the hepatitis C virus, Patriarca indicated.

"The hepatitis C virus has not been able to be cultured in regular tissue culture like many other viruses, and the only means of studying hepatitis C vaccines involves chimpanzees," he explained.

* Patriarca noted that chimpanzees cost approximately \$250,000 a year to maintain and study. "So what this means is there is the potential for some important vaccines where there will be pressure to put them into humans before they are adequately studied in animals," he said.

Another issue FDA is monitoring is the use of continuous cell lines, which "by definition have abnormal chromosomes either in number or the genetics of the chromosome," Patriarca said.

* While continuous cell lines are being used "for many good reasons" including their ability to be propagated and grow viruses to a high titer, Patriarca continued, "the worst thing we're concerned about is... malignancy, because some of these continuous cells even have the potential for growing tumors in laboratory animals."

Emerging challenges in new vaccine technologies underscore the need for a strong science base at FDA, Patriarca said.

The new challenges in the vaccine industry are "especially true" when dealing with live attenuated, vector-based or naked DNA vaccines, Patriarca said.

"There is the potential for these vaccines, many of which have been poorly characterized, to recombine with viruses that may be present within the vaccine," he added. "Some of these viruses are latent and persist for a while, so it's very important to assure that these things are safe before they are given to people."

These new challenges illustrate the need for a strong science base at FDA, Patriarca contended. If reviewers are allowed to conduct research, they will stay up to date on new advances in the field and provide a level of adaptability to emerging concerns, he said.

In addition to building stronger review teams, allowing FDA staff to participate in science will keep those reviewers happier and more satisfied with their jobs, the CBER division director suggested.

"I can tell you from personal experience that the worst job in the world is to be a reviewer," Patriarca said. "You're invisible, you get no credit, you're basically the bad guy. What this allows us to do is put some fun in these people's jobs and allow them to do science at the same time that they do review."

With reviewers actively conducting long-term research projects as well as addressing short-term safety problems, situations like the rotavirus intestinal blockage could be cleared up from within FDA, Patriarca suggested.

Patriarca cited the example of FDA scientists determining that the reverse transcriptase activity seen in measles vaccines would not pose a health hazard.

The ability to spot potential safety problems early on could prevent the type of negative publicity for the immunization program being seen in the mainstream media, Centers for Disease Control & Prevention National Immunization Program Director Walter Orenstein, MD, suggested.

As vaccines become more effective in preventing disease, the lack of perceived benefit has led to increased media attention to the negative events associated with immunization, Orenstein said.

"We are getting closer media and public scrutiny and it is likely to increase," the CDC official continued. "We are seeing for the first time in a long time, mainstream media getting on the vaccine safety bandwagon....What it means is we have to do a better job to monitor serious adverse events."

"We need a system to rapidly respond to allegations," Orenstein said. "The biggest nightmare we have is the allegation hits us first in the media with the absence of data, [like] 'autism is going up, vaccination is going up, hence vaccination must be causing autism.'"

With the diminishing funding being allocated for vaccine programs, CDC has not been able to devote the staff or resources necessary to adequately track adverse events "and see if they represent coincidental occurrences that occur when you give millions of vaccinations out, or whether they are truly causally related," Orenstein said.

Appropriations for Section 317 funding for vaccine programs have steadily declined since the start of the childhood immunization initiative, Orenstein noted, and while funds are shrinking, new vaccines are being added to the schedule, putting a greater stress on the delivery system.

"New and improved vaccines are on the way," the immunization program director said. "This is great because we're able to prevent more infectious disease, but what it also means is it puts a greater stress on the delivery system than we have ever had before."

Orenstein noted that the anticipated addition of Wyeth-Lederle's pneumococcal conjugate vaccine *Prevenar* to the immunization schedule will add four more

injections to the schedule for a total of 15-20 doses of vaccine before 18 months of age.

"So the delivery system is being overwhelmed by the technology which is not able as yet through combination vaccines to make it easier on the delivery system," Orenstein added.

Cuts to the 317 grant program have meant funding reductions of up to 50% for local immunization programs, leading to a decrease in quality assurance at the local level, National Association of County and City Health Officials Exec Director Tom Milne said.

According to a study published in the July issue of *Nature*, the loss of funding has resulted in clinic closures, increased waiting times, staff reductions and cuts to public awareness programs, Milne said.

Milne also cited an informal study done by the Washington state health department of physician office immunization practices which found that "in every office visited there were significant quality assurance problems," including "wrong doses, wrong routes of administration, wrong kid [or] missed opportunities for vaccine."

The most "outstanding glaring error" found on more than one occasion was powder intended for reconstitution with sterile water being thrown away and children injected with the water alone. "Now, this is not a backwoods community, this is a very typical traditional community," Milne explained. "If it's happening in Clark County, Washington, I can guarantee you it's happening across the country."

"Health departments serve an important function in assuring, or working to assure that the staff in physicians offices understand the need for quality control," Milne concluded. "So one can only suspect that as the publicly served clinics reduce the delivery of vaccines to their clients because of the loss of the 317 funds, that the impact of improper immunization in many physicians offices around the country is going to result in an even greater impact in terms of herd immunity."

The omnibus appropriations bill forwarded to the President Nov. 19 includes a total \$489.9 mil. for childhood immunization efforts at CDC, \$68.4 mil. above the House mark, but \$22.4 mil. below the Senate request. The bill also includes \$20 mil. for "polio eradication" and \$545 mil. for vaccine purchases for the Vaccines for Children program. ♦ ♦