said, "I have a group that looks at the adverse event data that come in. It is very frustrating not to be able to say that I really know that these events are coincidental, [that] they are not due to the vaccine. I really don't have good data to say that, and I would like to have these kinds of data."

Ellenberg estimated, for example, that "each year, 70-150 children can be expected to die of sudden infant death syndrome within two days of being vaccinated" based solely on the average rate of SIDS among American infants and the scheduling of vaccinations. Large vaccine safety trials could provide necessary data to differentiate between these "background" events and reactions actually tied to vaccination, she suggested.

Ellenberg told the DIA audience that a large vaccine safety trial could eliminate the need for Phase IV commitments.

"I think that the kind of study I would have in mind would probably get more patients than we do in a typical Phase IV study, and I think that it would resolve a lot of the issues that make Phase IV studies often required," she remarked. "If you did a big study in the first place that was very reassuring in terms of safety, that could really cut time off the development" of the vaccine, Ellenberg contended.

"The other advantage to [conducting trials] prelicensing is that with vaccines, because of the public health implication, it is virtually impossible to do any kind of a placebo-controlled study after licensure. Once a vaccine is licensed, the Centers for Disease Control is going to say that everybody should get it, and physicians are not going to be willing to not have children get the vaccine, even if there are these remaining questions."

Ellenberg also told the DIA session that large, simple trials could be valuable when the purpose of research is "to identify differences among potential treatment strategies that are meaningful from a public health perspective but are not likely to be detectable in smaller trials." Fellow panelist Gerald Faich, MD, Outcomes Research Corporation, similarly stressed the statistical power of such trials, adding that they could be conducted in a manner which is more representative of actual physician and patient behavior than a tightly controlled clinical study.

Faich argued that companies discussing a research protocol with FDA should not feel obliged to add all of the new requirements suggested by the agency. "I think FDA can add value to your protocol, and you ought to go in there and negotiate. But I think there are times you will need to stand your ground as well, because the folks at FDA are human and have some favorite things they would like to see studied too."

At the same time, research protocols are often overly complex due to misconceptions of agency expectations, Ellenberg contended. "I have had people call me up and say, 'We wanted to [run a research protocol], but our regulatory people or our CRO or somebody said the FDA isn't going to let you do that,'" Ellenberg remarked. "There was absolutely no problem with doing what they wanted to do. Somebody had decided that FDA wouldn't allow it, without anybody even coming to talk to the FDA. Yes, there is certainly a risk that FDA will ask you to do more than you had planned to do. But FDA may also confirm that you could do less than somebody else was telling you that you have to."

members agreed that use of the vaccines in children for therapeutic purposes rather than in a preventive situation changes the risk-benefit ratio and is easier to support.

A Merck representative from the audience asked FDA's Smith for "very, very, very clear guidance on what [FDA] really means by safety testing for vaccines." Merck's Ken Brown said: "I hate to see us go down the slippery slope of drug-style testing for safety issues," and remarked that he thought the issue of safety evaluations and FDA's expectations is "heading for disaster" without clear guidance for industry.

Smith responded, "I think one of the intents of the Points To Consider was to give the FDA and industry flexibility." He said that FDA is "very open to discussions at this time" and wants to be as "flexible as possible." He encouraged Merck Research Labs to comment on the document once it has been published.

Smith told the committee that there are three different plasmid DNA vaccine products in trials in four separate clinical studies. Committee member Mary Lou Clemens, MD, Johns Hopkins University, who is doing clinical trials in this area, suggested that her colleagues "keep an open mind and approach this as we would any other new technology." She recommended that investigators "inform volunteers about the potential risks" and engage other investigators doing studies "for assistance on helping define these theoretical events" that may occur.

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LARGE, SIMPLE VACCINE SAFETY TRIALS COULD ILLUMINATE WHETHER ADVERSE EVENTS are coincidental and not vaccine-induced, CBER Division of Biostatistics and Epidemiology Director Susan Ellenberg, PhD, told an Oct. 24 Drug Information Association meeting in Bethesda, Md. "This is my own proposal," Ellenberg emphasized. "It is not anything that FDA is about to go out and require you to do. But I think it is a useful thing to think about."

Noting that her division is "very concerned about vaccine safety," Ellenberg