

History
of the
U.S. Food and Drug Administration

Interviewee: Susan S. Ellenberg, Ph.D.

Interviewer: Suzanne W. Junod, Ph.D.

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Interview with Susan Ellenberg

December 7, 2004

TAPE 1, SIDE A

SJ: Today is December 7, 2004. We're here in the FDA History Office, Room 12-69, Parklawn Building, with Dr. Susan Ellenberg. What was your official title?

SE: I'm leaving as Director of the Office of Biostatistics and Epidemiology in CBER (Center of Biologics Evaluation and Research) and I've been in the same position except that it was a division when I started, and now it's an office.

SJ: We just want to talk today about your career at FDA. You've worked during a very interesting time for Biologics, and we wanted to get your perspective on some of the changes you've witnessed and obtain your perspectives on some of the problems that you've worked on.

SE: Okay.

SJ: So tell us, where were you born and . . .

SE: I was born and grew up in Tucson, Arizona, and my family, my sisters and my mother are still out there. It makes me happy in the wintertime when I can go out to visit

them. I lived there until I went away to college.

I went to Radcliffe College in Boston, and after I graduated, I got a Master of Arts in teaching. I grew up never wanting to be anything other than a teacher. As I went through high school, I learned that what I could be most happy teaching was mathematics. I really loved math, and I got a master of arts in teaching, an M.A.T. degree. As an undergraduate, I had been working in Project Upward Bound, which was sort of the high school version of Head Start in the Cambridge Public Schools. After I got my M.A.T., I taught high school for three years, one year in Cambridge, Massachusetts, and then two years in Montgomery County. And through a long series of accidental, unexpected kinds of things, I ended up going to graduate school in statistics rather than ultimately going back and being a high school teacher.

SJ: And where was your statistics degree from?

SE: From George Washington University here in town. I started after my first child was born. The GW graduate program is ideal for people who work for the government, who work full time, so the courses are at night, which was fine for me. My husband was working for NIH. He'd come home from work and I'd go to school. So I was really very fortunate compared to a lot of women who struggle with family versus career. I took my courses at night and was able to get in homework during the day when the kids were sleeping, and it just, it took me longer. I mean, from the time I took my first course till the time I got my degree was eight years, but that was okay. I got to be home with my kids most of the time when they were very young, and I didn't have to make the kind of

hard choices that my daughter and daughter-in-law are going to have to make and so many others have to make these days.

SJ: And tell us what brought you to the FDA.

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SE: How I came to the FDA. Well, actually, I should go back.

When I was getting my graduate degree, I was also working for a very renowned biostatistician who had retired from NIH. His name was Jerome Cornfield. And one of the first tasks I worked on for him was a contract that he had with Chuck Anello, who was then a young statistician here at FDA and who wanted a program to do the kind of sequential analysis of clinical trials that Jerry Cornfield had developed. It was from a Bayesian perspective, and that was like in the early 1970s. We hear a lot about Bayesian statistics now. Former Commissioner McClellan was very interested and we had a big conference last spring, but thirty-some years ago, Chuck Anello had been looking into this to see if there was a role for the methodology. I remember walking down the halls of Parklawn with my son in a stroller -- it must have been 1973 or '74 -- bringing this computer program to Chuck to show him how to run it. I remember thinking, how do people work in this building? I mean, I'm walking down the hallway with my kid in the stroller, and there wasn't room for anybody else to walk past.

JS: I had a similar experience in the mid-'80s, before I came to work here. I visited this building and I thought, oh, my God.

SE: That was actually my first experience with the FDA as well.

Male: You were working as a contractor?

SE: I was working for George Washington University at the time, part time, but Cornfield had a contract with FDA to develop this methodology and to then, obviously, write the program. But I eventually came to FDA. I was working at NIH, first in cancer research and then in AIDS research, and I was at the Division of AIDS at NIAID (National Institute of Allergies and Infectious Disease) starting in 1988, and I began to work much more closely with the FDA than I had ever had before because AIDS was so new and there was so much emotion and so much urgency about AIDS drug development. This was like nothing anybody had ever seen before. People were realizing the need to invent new ways to do research and new ways to regulate.

We worked very closely with -- when I say we, at NIAID, worked closely with FDA. Carl Peck was head of CDER then, and after Ellen Cooper, who'd been head of the antiviral group, left, Carl actually became Acting. So he was the Center Director, but he was also an Acting Division Director because he really wanted to make this go. We would have weekly meetings, the Division of AIDS staff, with the Antiviral Drugs staff at seven in the morning because that's the time Carl started his day, and that was the only time we could fit it in. We had weekly meetings from seven to eight over in the building on Nicholson Lane next to White Flint, which was where the Antiviral Division was at that time, to talk about what was going on with the AIDS Clinical Trials Group and what new studies were starting and what was going to get started, and to make sure that we

were sharing enough information so that we wouldn't end up with delays in getting drugs approved or even getting initiated because there were some misunderstandings between the researchers and the FDA. The FDA needed to understand why the study was being designed in such a way or what the issues were so that they could avoid delays. That was very exciting. And, of course, there was all the controversy with the AIDS activists.

And a statistician at CDER (Center for Drug Evaluation and Research) -- I think he's still here, Satya Dubey, suggested to me one time that we start an informal, regular meeting of statisticians interested in AIDS research to talk about some of the issues, because there were huge controversies as to how these studies were being done. If you remember, the activists were saying, oh, no placebos and no this, and you've got to have this and have it this way, and you have to have humane studies and all of this.

Everybody agreed we have to have humane studies.

So we agreed with that, and we started a regular meeting, which ultimately the activists became involved in. It was just a wonderful period of a few years when I think I must have felt a little bit like physicians who go and work in Third World countries, where you have to sort of figure out what you're doing minute by minute and you're saving lives, and you feel like you're really doing something for the world. That's kind of how it was, where we had the Act Up people and statisticians from NIH and FDA, even people who weren't involved in AIDS research on a day-to-day basis, people of other parts of NIH who wanted to contribute.

And, of course, the statisticians who were part of the statistical centers for the AIDS groups, the Harvard group who had the statistical center for the AIDS Clinical Trials Group, and some of the Minnesota people who had the statistical center for the

community clinical trials group. Some of the physicians who were more interested in study design, they would come.

We started off with a meeting of maybe twenty to twenty-five people. We met four times a year in conjunction with the AIDS Clinical Trials Group meeting, and within a couple of meetings we had 100 to 120 people, and we had activists and clinicians and statisticians, and it was very lively. I would invite people, statisticians and others, who had interesting ideas about study designs to come and present. I asked some of the top people in research anywhere. Nobody ever said “no,” they weren’t going to come to this group.

SJ: Did you have a formal title for the group?

SE: We called it the Statistical Working Group, and it just was very informal. We had these meetings. They were going on for a year before the activists were welcome in the clinical trials meetings. So I think we were a little bit pioneers there.

I still haven’t gotten to the point where I was leading to with all this. Your question was how I came to FDA, so at this time in AIDS when we were working so closely with the FDA and on development of new issues and how to get drugs approved fast, it was very motivating.

So when the new position in Biologics came up, and there were people there who asked me -- I had actually just agreed to serve on the Biological Response Modifiers Advisory Committee. But it was all because I’d become known to the FDA through the AIDS stuff, and I decided, well, it might be interesting to work on this side.

JS: You mentioned the challenge to statisticians in dealing with this unique problem of crafting drug studies in a way that would be statistically sound yet responsive to the immediate clinical needs, as spoken to so forcefully by the AIDS community, Act Up and others.

SE: Yes.

JS: How do you broker those two, what seemed to be pretty difficult sides to bring together?

SE: Actually, it was not so difficult. That was what was so beautiful about it. I remember going to the international AIDS meeting in Montreal in 1989. It was my first interaction with the activists, and they were there dressed in their most provocative style handing out this brochure. It was called The Treatment Agenda for ACT UP, and it was a fifteen- or twenty-page Xeroxed document. I took one and I started reading it, and I found myself scribbling furiously. My notes were like, “You mean that’s not how it’s being done?” “You mean the studies aren’t like that?” “Why can’t . . .” Most of the things they said were very sensible, and you could do studies in the way they proposed. It was just not the traditional way that companies had done clinical trials, at least in infectious diseases. There were things that they weren’t used to.

For example, it’s pretty standard in a lot of the areas at FDA, when you do a clinical trial of a new drug, you don’t want people taking other drugs at the same time

because it might interfere with the action of the drug or there might be an adverse reaction. If there's an adverse effect, you don't know which drug is causing it. And so companies like to keep things very clean and pure.

Well, when people have a life-threatening disease, you can't say to them, "You can't take anything else." In fact, you should question whether you would even want to do that, because you want to know -- it doesn't do you any good to know whether it works in one context if it's going to be used in this other context. You need to study it in a way that it's going to be used. And in cancer, while I was involved in cancer research for ten years before, we didn't have any such restrictions. People got the normal things that they got, and people didn't try and make it all tight. The question was, if you added new drug X to the standard regimen or everything else people might be taking, all in all, was it better?

Then there were things that were just non-standard and new. There were new drugs being developed for -- there were antivirals, and there were drugs to prevent or to treat opportunistic infections. Because the disease was so new, lots of the most promising treatments were not yet approved. They were in trials. But people wanted to be in more than one trial at the same time, and there was a lot of resistance to that because it wasn't the way things were done. The first instinct is, well, how are we going to sort things out?

But my feeling, and the feeling of a lot of other people, was that first you have to decide what's best for the patients. You have to make sure that you're treating everybody as effectively as you can treat them. Then you worry about how you're going to sort it out. You don't say somebody's going to get, or somebody is more likely to die

because you couldn't get the right statistical design. The people who were putting patients on trials are people who are treating those people for a life-threatening disease, so once you got into the mindset that first you have to make sure all the patients are fully treated . . .

I don't mean to suggest that there were people who really didn't think patients needed to be properly treated. It wasn't that way at all. It was just, it was a little bit like when I started working in cancer studies after I had been working more in the heart disease area, that was a culture shock, too, because in cancer studies, people were much more loose about a lot of things related to study design. There was a recognition that people were going to have their standard treatment and you were going to try this, but things weren't controlled as rigorously. There were different cultures. So the cardiovascular people thought that the cancer people were impossibly sloppy and couldn't figure out how they could ever learn anything about what they were doing, and the cancer people thought that the cardiovascular people were ridiculously restrained and were testing in situations that weren't generalizable. Neither of them was right. I mean, you have to test things different ways in different arenas.

One of the things I've learned over my career, working in different disease areas and also working, first working at NIH and now FDA, is that people develop truths based on their own experience, and find it sometimes very hard to see that what's absolutely true for them or what they believe to be absolutely the right way to do things may not apply in other areas. It's not an absolute truth. It may be a strong truth for this particular area.

JS: That's where statistics comes in, though, right?

SE: Well, I don't know it's so much as where statistics comes in, but it's where you need people who have had a broader kind of experience to recognize. Sometimes the statistician plays that role because a statistician often will have experience in multiple different diseases and can say, "Well, wait a minute."

A few years ago, there were -- well, more than a few; it's been going on for some time. But there's been controversy about the appropriate use of placebos in clinical trials. This is an area that I've gotten involved with a lot with Bob Temple. People will say, "But if there's an existing treatment, it's unethical to test with a placebo treatment. How can you do that?" The people who say that for the most part are people who spent their lives working in studies of cardiovascular disease or cancer or AIDS or some kind of life-threatening disease, where it is unimaginable to use a placebo control.

If you have an effective treatment that we know on average saves lives, you don't compare a new treatment with a placebo. You test a new treatment to see if it's as good or better than the treatment that you know has some effect. But those people often have no knowledge whatsoever of the world of clinical trials for a rhinitis drug or headache drug, because the people who write articles about methods for clinical trials tend to be in the academic setting, and they tend to work on NIH grants and they tend to work on the more serious diseases with serious outcomes. I actually have a slide and talk I give about this to point out that the vast majority of clinical trials that are done are done of drugs to treat symptoms. They're not done on new treatments to save lives or preserve function in degenerative diseases. They're done to treat stomachaches and headaches and rashes and

itches and hair loss and all kinds of new things that we didn't even know about ten or fifteen years ago, new diseases. So in those kinds of studies, it's hard to make a case that there's any real ethical issue of putting patients at any kind of risk, as long as they're fully informed, in a placebo trial. But you have this huge outcry because people are thinking about, oh, people are dying, and you're going to give them a placebo.

JS: You mentioned comparing the way trials were conducted with cancer drugs, for example, and obviously other life-threatening diseases.

SE: Yes.

JS: Were there specific ways that you took from those studies -- ways that the construction of studies or ways that you could evaluate AIDS drugs, for example? How did you learn from the cancer cases the way cancer drugs are evaluated?

SE: Well, that was important, and for the most part, infectious disease physicians doing studies -- not 100 percent but most of the studies that were done, you know, new antibiotics, things like that, it was a short-term treatment. You would do a culture and you would see that the person had the bug that you were interested in treating, and then you would treat them for a week, two weeks, three weeks, whatever the course of treatment was, and then you would do another culture and you would see whether you got rid of the pathogen, and that's how you did studies.

In the beginning, when people were testing AIDS drugs, that's how they wanted

to test them. They wanted to find something that was equivalent to the pathogen and see whether they could eradicate it in a short period of time. So initial studies were done using, in addition to CD4 count, which got to be used more and more, there was something called P24 and there were a variety of other markers that people were looking at.

Now, people who had had some experience with cancer -- and there were many AIDS physicians who actually were oncologists because one of the first manifestations of AIDS, perhaps the first one that was recognized, was Kaposi sarcoma, so it was the cancer docs who were aware of that first, even before I think people had identified it as an infectious disease, and they recognized that these needed to be long-term studies. By the time we knew what we needed to study, we knew people were dying, and we knew we were going to need to follow people for survival, and that was something that the cancer community was used to doing.

The person hired to run the AIDS studies at NIH came from the National Cancer Institute, and there was a lot of tension along the way between -- there were infectious-disease doctors who resented having the "cancer model" being thrust on them. The truth was, obviously, you needed to develop something in between. You needed to be able to follow people for a long time. As much as people wanted to have a surrogate endpoint, a surrogate marker, if you couldn't really rely on it, it wasn't going to help anybody, and I was impressed at how quickly the AIDS activist group picked up on that and stopped calling for approving drugs early based on surrogates. I mean, at least in the beginning.

Now, of course, people measure viral load and they approve antivirals, but we have a lot of information now on how that works and how that predicts, and people are in

fact living much longer. But the AIDS activists actually became the strongest allies for good science and really wanting to know. They knew it wasn't going to help them to have a medicine chest full of drugs if they then had to guess which ones might work and which ones didn't. They knew that they needed the data on which ones worked and which ones didn't, which ones were going to prolong life and which ones would not. There were certainly some surprises along the way in that regard.

SJ: Do you remember any that are worth noting?

SE: Well, see, now I'm going back and we're focusing on my pre-FDA time. I remember one. I remember one case where they were testing a drug for CMV retinitis, which is an eye disease, a very serious eye disease, and people can become blind. There had been a drug that had been approved, and they were testing a new drug compared to that one, and the primary endpoint was related to vision. The study got stopped early because there were more deaths in one of the arms.

So I remember a colleague telling me, when she brought her patients back in to tell them the study's been stopped and to tell them that one of these drugs, you know, which one they were on, and I remember her telling me that the first person was told that they were on this drug that had been associated with actually a six-month-longer survival time than the other drug, that it had a lot of toxicities, and he said, "You mean I've got to live six more months with feeling this way?" I mean, it was really, it really brought home how, even for people who have a life-threatening illness and who are facing death, that the quality of life is not a trivial issue, and not everybody is willing to be miserable

in order to gain a few extra months. I don't think that drug actually became widely used because it was so highly toxic.

SJ: Tell us a little about being recruited and coming over to FDA.

SE: I had been asked to be on the Biological Response Modifiers Advisory Committee, and I had served on it once or twice as a guest statistician. I'm not sure that CBER had routinely had statisticians on their advisory committees in those days, except maybe for vaccines.

I remember that one of the products that we looked at when I was on the advisory committee was a sepsis drug, I think, made by Xoma, and I remember being very puzzled by the analyses that were presented because it didn't really look like -- I think it was either a historical control or it was something that was, it was very fuzzy. It was not a rigorously done trial where everything was pre-specified as to what you look for. But this was a whole new area for me. I mean, having gone from cancer, from cardiovascular disease to cancer to AIDS, I'd very much recognized how different things could be in different areas. There are things that you need to learn about -- you recognize that *maybe* you're not fully understanding what it is they're presenting. So I remember that.

The drug ultimately was not approved, but there was a lot of enthusiasm on the committee, I remember, for it.

Then I was asked to actually be a permanent member, and at the same time they advertised some positions. Apparently, when Drugs and Biologics had been together and then they split apart in the late '80s again, but after they split apart, the biostatistical and

epidemiology functions for CBER stayed in CDER. I guess they felt it was going to be too small and that it would be better just to keep it as part of one group. But after a few years, CBER really wanted their own group. They wanted that group to be part of CBER, and so there was an agreement to establish a CBER Division of Biostatistics and Epidemiology, and they recruited for a director.

A couple of people that I had interacted with either through the Biological Response Modifiers Committee or possibly even through other things, maybe AIDS vaccines, which were in their infancy, and I guess still are in their infancy, but a couple of people had said that they hoped I would apply for this job. At that time, I was incredibly committed to AIDS research.

One of my close colleagues from the National Cancer Institute had been diagnosed with AIDS just at about the time that I went and took the job, and he became very involved with the statistical working group that I mentioned. In fact, he became a very strong leader because he was gay and he was very, very smart. He was one of these sort of renaissance-man types who was a musician and an artist and he was a physician, and he functioned as a statistician, but he was self-taught. He had never had a statistics degree. He had an M.D. His name was David Byar, and he was just a brilliant, brilliant person.

So I was very committed to AIDS research, and it was hard to think about moving on.

But there were some frustrations. There were some growing frustrations, too, in that job, and I did start to think about whether I wanted to maybe do something else. Then the CBER job was advertised and there were a couple of people that had

encouraged me to apply, and so I did. I was selected, but I still wasn't sure and I was vacillating. Kathy Zoom had been telling me, "You're got to make a decision. We're going to lose the slot. You've got to make a decision."

I remember coming to see Kathy with my decision. I was working on a presentation about testing HIV vaccines, new HIV vaccines. There was going to be a big meeting about it that Bernadine Healey, who was then head of the NIH, was going to be at, and several of us were working with [Anthony] Fauci on presentations for this big workshop. I remember at some point, in preparing for that, I just somehow made the decision. When this rehearsal was finished, I walked across the campus to her office and said, "I'm coming." She gave me a big hug, and I thought, well, this is nice. That never happened to me in any other job.

I had work I really wanted to finish at NIH, and they made an arrangement that I would be on the books at FDA starting two months before I was actually there, because Kathy was afraid she would lose the slot. Then I was essentially detailed back to NIH to finish up my work.

JS: Where was the division situated administratively?

SE: Biostatistics and Epidemiology.

So when CBER and CDER split, CBER, I think, was at that time divided into the -- there were two offices, the Office of Biologics Research and the Office of Biologics Review, and they decided in, I guess, '91 or '92, they were . . . They didn't have a permanent director, and ultimately -- I'm not sure of the timing. It must have been that

Kathy Zoon was finally selected as the director, and then she led a, you know, sort of a strategy session of the senior leadership and developed a reorganization. In that reorganization, three product offices were established: therapeutics, vaccines, and blood and blood products. Then there was, of course, an Office of Management and an Office of Compliance, and they had an Office of, it was often called the office of other things or miscellaneous stuff, and it was called the Office of Establishment Licensing and Product Surveillance, or OELPS, and that office was headed by Jerome Donlon, who had been head of the previous Office of Biologics Review. That was before my time there.

In this office there was the Product Quality Group. Those were the people who went off and did inspections. Then there was the Laboratory Group that did assays like potency testing. There was the Veterinary Group, people who took care of the animals that were involved in the research program. I thought there were five of us, but I'm blanking on the last one. Then there was us, Biostatistics and Epidemiology. Our interactions were really more with the product offices than with any of the other divisions in my office.

I remember when I was hired for the job, I was a little concerned that at that level, I wasn't going to be having direct access with the directors of the product offices, and Kathy said, "Well, look, we just finished this reorganization." She didn't want to start up anything new. She said, "Give it a try," and if I felt that it wasn't working, I should come back to her and see. But it actually turned out just fine.

I didn't have any trouble talking to the people that I needed to talk to, and I was very fortunate in being able to hire some very good people, and we gradually built a division. There were, I think, about eighteen or nineteen people in that division when I

came on board. And at the time of the 2002 reorganization, we were up to about fifty, I think, and now we're down to forty, having lost a big chunk of our statistical group to CDER. So it was built up partly through PDUFA [Prescription Drug User Fee Act] and just partly through people recognizing that more support was needed.

So that's the structure.

SJ: What were some of the issues that you faced? I mean, we want to explore case studies, if you care to do it that way. We want to get a sense of the growth, the changes that the organization had that you . . .

SE: Well, there were some interesting things early on. There were people in the Center who saw me as someone who could be an ally when they thought things weren't being done properly or the science wasn't good. Early on, I got pulled into a particular application that was actually quite interesting.

NIH had sponsored a study of a type of immune globulin that would prevent respiratory syncytial virus in children who were at high risk of bad outcomes from RSV infection. RSV is a fairly common infection, and most kids will get sick but clear it. But if a premature baby gets it or a kid with other kinds of problems, it could be very, very serious. And immune globulins are often used to protect people whose immune system may need a little more stimulus.

So this infusion immune globulin product had been tested, and I think, actually, somebody had gotten a grant. It wasn't something that NIH itself had decided needed to be tested. Somebody had proposed a grant, and it was a Phase II study, it was being done

in five centers, and it wasn't a blinded study. It was an infusion study in premature and other sick infants. The idea of doing that blinded, infusing saline solution, a non-active agent, in sick babies, you think to yourself, do I really have to have a placebo in this study, and is it really that important to have it blinded? So it wasn't blinded, and it wasn't being done, it wasn't being overseen by somebody who really knew regulatory procedures or even had any strong sense of how to do clinical trials.

But the study came out very positive, and it was published in the *New England Journal of Medicine*, and there was an editorial saying, oh, it's the most wonderful thing, isn't this great, we finally have a therapy that's going to help these poor kids.

Well, in the meantime, our bioresearch monitoring (BIMO) people had gone and looked at the various sites participating in the study, and it found all kinds of things that were very, very problematic. One major issue related to study dropouts. The study had been reported to have been analyzed according to "intention to treat," which means that if you were randomized into the study, you were going to be analyzed in the group that you were in, even if you didn't finish getting your treatment. This approach prevents a known way that studies can be biased; people stop when they start getting sick, they stop taking the treatment, and in the most severe case, somebody dies after they have a course or two of the treatment. And then, if you throw them out and say, "Well, they don't count because they didn't get the full course of the treatment" -- but they died, you know. So the treatment didn't do them any good. So that's sort of the extreme version of it.

So in order to avoid bias, you need to make sure that you count everybody who is assigned to get the treatment.

But the BIMO inspectors found evidence of lots of people who were randomized

into the trial but not reported, and there were all people who had been randomized to get the treatment. None of them were randomized to the untreated group.

JS: Who was the sponsor of this?

SE: The study was funded by the National Institutes of Health, but it was a grant, so it didn't have much actual oversight from NIH. I should emphasize that none of this was being done deliberately to try to fool anybody. The problem was that the study was being done by people who really wanted to test this but didn't have a lot of experience in conducting trials, and so they made a lot of mistakes.

Another kind of mistake that they made had to do with the process of randomization. Because it wasn't a blinded trial, each separate center was doing its own randomization. So the nurse who would do the randomization was the one who actually was talking to the parent, and that nurse would have known, because it wasn't a blinded study, whether those parents' child would be randomized to the treatment or the control arm. So that could be a possible bias -- right? -- because she might choose not to randomize a child who was really sick and was not going to get treated, maybe she wouldn't randomize them, or maybe she wouldn't randomize them if she thought they *were* going to get the treatment because she didn't think the treatment would help them, and why should they get burdened with all that treatment. There are lots of ways it could work, and there was no evidence that the nurse had in fact done anything like that. You can't find evidence to show that somebody's been influenced. But you can't rule out the possibility that some selection process was operating that would bias the trial.

When you do clinical trials in a rigorous way, you protect against such influences.

If it's an unblinded study, you have the randomization process be done by somebody who doesn't know what the next treatment is going to be.

So there were a number of things like that that were simply due to inexperience with doing and managing clinical trials, but there was enough of those problems that I personally felt I wasn't sure that I could believe the results of the study.

There were also some other issues. There were four or five deaths, five or six deaths in the study, and they were all on the active treatment arm. That isn't quite as bad as it sounds because there were actually two treatment arms, a lower dose and a high dose, and so you would have expected a two, two . . . Well, I'm not sure whether there were two doses or whether it was a 2:1 randomization or whatever. If there were six deaths, you would have expected 4:2, treatment:control. Instead, you had 6:0. So it could happen, clearly possible by chance, but there were some other things like that that were worrisome.

JS: Now, these irregularities were such that you wouldn't have expected the people involved in these to realize that these were indeed irregularities in a statistically sound clinical evaluation.

SE: Well, I would have expected -- there were enough people involved who, like the people at NIH, who paid for it. There were people there who were knowledgeable enough to recognize the problems. But, again, it was being done as a grant, not as a cooperative agreement or contract, so there wasn't that much NIH oversight of it. In the middle of the trial, it was taken over by a manufacturer, who decided that they wanted

rights to this product and they were going to develop it and sell it. So it was the manufacturer's decision to push and to try and make this into a licensing application.

When the data were presented at the advisory committee, the advisory committee ripped it to pieces. They were very devastating. They were very concerned about what we had shown about some of the problems in the trial.

So that was an interesting introduction.

At the end of all of that, I pushed for us writing a letter to the *New England Journal of Medicine* because I felt that, here they'd published this article that was very, very positive, and then they'd published a go-with editorial that said this was great. Then there's this advisory committee where there's a unanimous vote against approving the product, and the FDA doesn't approve it. I felt like there needed to be something in the literature that if somebody did a literature search, some kind of explanation would come up. And there was not a unanimity of opinion within CBER as to whether we should really write such a letter. After all, when you don't approve a product, there isn't a finality to it. You don't issue a letter saying, "I'm not approving it," like you issue you a letter if you are approving it. Usually you tell the sponsor what they need to do, and it might stay open for a while. Anyway, there was a concern about whether we could write something given that this was open, and should we write something, and what was the point of doing it.

I think there has not been a strong culture at FDA of writing articles that have regulatory implications, writing about decisions that were made, things like that. I mean, in CBER, there's a strong tradition of research and writing and publishing papers, but there was not a strong tradition of writing about the regulatory aspects of what we were

doing. I actually thought that was pretty important because my experience from watching the FDA from when I was at NIH was that I didn't understand why FDA did a lot of the things that they did, and we'd have these statistical working groups sometimes, and statisticians would make arguments. The position of the FDA statisticians sometimes seemed off-the-wall to me.

One of the things I learned quickly when I came to the FDA was that, while there were some things I still disagreed with, there were many things that I had thought were bad which I came to understand what the reason was as to why things were done that way, and I came to agree that's the way they should be done.

I'll move away from the therapeutic products. One of the big areas I had to learn about when I came on board was epidemiology. It's the Division of Biostatistics and Epidemiology, and I'm a biostatistician. I knew a lot about clinical trials.

But what's this epidemiology part? Well, epidemiology in FDA is post-marketing surveillance, very much in the news now. I didn't really know very much about this. What I did know when I came on board was that there was a lot of controversy over vaccine safety and how the post-marketing reports of vaccines were being looked at, and there had been some meetings, maybe with congressional staff or whatever that had not gone particularly well for CBER, and which was something that was high on my priority list, to see what we were doing about vaccine safety. So that was something I got interested in. We developed an overview of what we were doing and worked with the CDC [Centers for Disease Control] on the adverse-event reporting system for vaccines, which is separate from the CDER system.

As I started looking into this, I came to the realization that we really didn't have

very much information at all from the clinical trials. The vaccine clinical trials, people who did vaccine trials -- I was talking before about different cultures and different areas, so vaccines were really their own culture. Everybody, all the people who worked on them believed that they were safe, and they understood how they worked, and trials were often very small, and sometimes not even terribly well controlled. A lot of the vaccines that had been approved had been approved even before 1962, before the requirements, before the efficacy requirements.

I looked at this and I thought to myself, "We've got parents out there who observe something bad happening to their child shortly after they get a vaccine, and they're perfectly rightfully concerned that maybe it was something about the vaccine. The birth cohort in the United States is 4 million a year, 4 million healthy babies born every year, and all of them are going to get multiple vaccinations in the first few years of life because vaccination is essentially mandated in this country. You can't send your kid to public school or into daycare centers unless they're vaccinated. I started asking questions about why don't we demand more data, more data on safety before we approve these vaccines? Why should we approve a vaccine on a handful of safety data. Even if -- we can do a study with 300 kids and tell that the vaccine works. If there was a one-in-a-thousand serious adverse event, that would be 40,000 kids a year that would experience that. Shouldn't we know more about safety?"

Bud Anthony was the head of the Division of Bacterial Products then in the Office of Vaccines, and we'd been talking about this issue, and in 1994 or 1995 he asked me to make a presentation to his group, and I think people were just horrified. That's probably the best word for it. I don't know. I might as well have said to them, that we

make a new rule that vaccines should all be administered by people in clown suits with red noses or something like that. That's how much sense it made to them.

The more I thought about it, the more sense I thought it made that, if we had vaccines that we were going to expect everybody to take, and people needed to take them to protect not just their children, but the children next door or the children down the street because of herd immunity, that maybe we owed it to parents to at least have the data to show that the vaccines weren't causing sudden infant death and they weren't causing autism and they weren't causing diabetes and they weren't causing . . .

I calculated that if you did trials for a new vaccine of 50,000, which is not an unheard-of number for a clinical trial, even a vaccine trial, but it's not common, you could pretty much rule out a doubling of most of the kinds of adverse events that people have associated with vaccines.

This idea was certainly provocative, but it didn't win a lot of adherents even within the FDA. I didn't really talk about it too much outside. I mean, this would be something that would clearly, could clearly cause a lot of anxiety and controversy, and I didn't feel it was appropriate, on my own, to go and raise these issues out in the world when I knew that this was not something that most of the people at the FDA would support. It would certainly generate a lot of anxiety in industry, and not just in industry, among people who did vaccine studies, because it was basically saying that maybe things haven't been done appropriately or maybe it would suggest that maybe there were bad side effects with vaccines. But I felt it was really the right thing to do.

And then the rotavirus vaccine experience happened. Are you familiar with that? That was a vaccine that was withdrawn by the manufacturer less than a year after it was

approved because of its association with this bowel problem, intussusception.

In the wake of that, suddenly I was no longer considered both crazy and dangerous on this topic. I think I was still considered dangerous, but maybe not crazy. And Kathy Zoon asked me to organize a workshop to talk about how big should vaccine clinical trials actually be? So we did that. We had a workshop, an international workshop, in the year 2000, and we had a lot of people come and talk about how much safety data should we have on new vaccines before they were rolled out? I certainly will not tell you, because it would not be true, that the meeting resulted in everybody coming to agree with me. There did seem to be some recognition that maybe moving to new orders of magnitude so quickly was not the best way to do it. To do studies in hundreds of children and then suddenly be vaccinating millions of children, maybe there should be something in between.

Now, that is still an idea whose time has not come, although what my colleagues in the Office of Vaccines tell me is, because I'm getting up there talking about trials of 50,000 or 100,000, if the vaccine manufacturer comes in and wants to do a study in 200 kids and they say you need 500 kids, there's not as much protest as there used to be.

But the idea is out there. Actually, it took a long time. We took a transcript of the meeting and we wrote it up, and it's going to be published in *American Journal of Public Health* pretty soon.

I still believe that is what we should do.

I should say that I think what you need is the randomized comparison. What was pretty common was doing a small, randomized trial for efficacy and then vaccinating another 8,000 or 10,000 kids without a control group, just to make sure nothing really

terrible happened. But the problem is the kind of things that have been associated with vaccination by parents are things that are not so uncommon. So if you just vaccinate all the kids without a control group, and then you have some of those kids, ten or twelve become diagnosed as autistic, well, what do you know? You don't know anything. You don't have the evidence that there's more or fewer or the same kids who are autistic who took the vaccine and who didn't take the vaccine. So unless you have a control group, you can't really assess these kinds of alleged adverse reactions.

It's much less difficult when you're first testing a vaccine when it's new. Then you have to have a control group. People understand that you can't evaluate efficacy without a control group. But what they have not understood is that you often can't evaluate safety with a control group either.

So that's a battle that I have fought and have not won.

JS: Well, it's ironic considering what you're raising here, the fact that the Center has been sued or subject to suit on so many of these issues over the past several years.

Right?

SE: Sued?

JS: Well, not sued, but that these are issues that parents -- you mentioned autism.

SE: Well, there certainly has always been a lot of concern about vaccine safety, at least for the last twenty or so years. But here's what happens.

You have 4 million kids and they're vaccinated at birth and at two months and at four months and at six months and a year. And you look at some of these kinds of diseases. There are things that happen early in a child's life, within the first year or two, so if you vaccinate everybody, then everybody who develops any of these bad things is going to develop it after a vaccination. Since vaccination doesn't protect against those things, it's going to happen in some cases that those things are going to develop in close proximity to the time somebody was vaccinated. So, sudden-infant-death syndrome (SIDS), for example. You have 4 million kids vaccinated a year. The rate of SIDS is about one in 1,500. So it's going to happen that there's going to be some SIDS deaths within a day or two after a vaccine, by chance, and it's not going to be one or two. It might be fifty in a year. It's just because, any given day, there's going to be a certain number of SIDS deaths, and the vaccine doesn't protect against SIDS, so it's not the case that the first day or two after you're vaccinated is a protective time against SIDS. You're going to have some of those coincidental happenings.

So what do you make of it? If you're a parent, it's very hard to believe that one didn't have anything to do to the other. If I tell you that's going to happen fifty or 100 times to babies because there are so many kids vaccinated and SIDS is not so uncommon and it's a coincidental finding, you know, that mathematics is not going to impress them. But my feeling is what we need to do is have the data, so even if we are never going to convince that particular parent, we're going to convince people who are making vaccination policy and deciding whether to vaccinate their children to show them that, "Look, we did the study, and we had the same number on the vaccine and the same number on the placebo. There's no association."

It's a little bit like the situation we had with the Lyme vaccine, which is another vaccine that the manufacturer withdrew, different in that there was never strong data like there was with the rotavirus vaccine to show that the vaccine was really causing any problems. There were a lot of people who felt they had arthritic-type problems after the Lyme vaccine, but in the clinical trial that was done of the Lyme vaccine, there were exactly the same number on the vaccine and placebo who had arthritic problems following their injections, whether it was vaccine or placebo. So you knew, once the vaccine was out there, there was going to be some people who were going to have these problems, and you can't tell whether anything was due to the vaccine or not.

SE: Well, on pneumococcal vaccine, there's age. I mean, it does, the older you get, the less prone you are. The vaccine was not as effective at preventing ear infections as people had hoped. Vaccines are generally not even considered for approval unless they're at least 70 to 80 percent effective in preventing an infection.

The pneumococcal vaccine was highly effective in preventing invasive pneumococcal disease. Its level of efficacy for the ear infections, however, was 8 percent.

SJ: Eight percent?

SE: Eight percent.

So it prevented a very small number of infections. I mean, it was statistically significant. It prevented some, but it prevented a small proportion.

Now we're in the genomic era. We're all starting to believe now that there are

certain people who respond better than others -- or who may not respond -- due to something in their genetic make-up.

One of the things that we've done with regard to post-marketing surveillance is that we make it a practice to publish a paper within two or three years after every new vaccine is approved. We review all the adverse-event reports that have been sent in and try and make determinations to whether any of them represent a likely really new reaction to the vaccine.

TAPE 2, SIDE A

SE: So, because of all the interest in vaccine safety, one of the things that I decided to do early on was to make sure that after every new vaccine was approved and there was some experience, we would write a paper describing the kinds of safety reports that we had gotten for this vaccine, and we would look at the reports. And the reports that come in, you know, parents will send in reports, physicians or nurses or other people will send in, this vaccine was given and this happened. We encourage people to send in those reports, even if they don't know for sure that the vaccine caused the problem. But, gee, we gave the vaccine and this happened. Could it have been related? And, you know, if you get enough reports, maybe you'll see something. So that's what we do.

The majority of the reports that come in are not-so-serious things. They're swelling or somebody was fussy for three days instead of the usual few hours, or they ran a fever, a high fever. Those are things that you pretty much believe are due to the vaccine, and you observe them in the clinical trials and you know that they could be a

problem.

Then you have the more serious stuff , like autism and SIDS and other kinds of things where there's no obvious connection with the vaccine, but it did happen afterwards, pretty close, and so you do want to think about it. In some of those things, maybe there is a little more of a biological rationale, and so we look into that and think about it and see whether there's any other information that you can get that might support a causal connection.

Then we write this up. We've had good success in getting these reports published. My feeling has been that, first of all, our job is to look at those reports and to see whether there are any new adverse events that need to be in the label that people need to know about, so we're doing our job when we do that. But to write it up and put it out in the literature tells people, suppose there is something new. It'll go on the label. Will people really see that? What we're doing by putting it in a journal article is ensuring that more people are aware of it.

What actually happens, though, because most of the time you don't find some kind of new adverse event, but we show people what we did find, so we're telling people that we're looking at these reports and that we're thinking about them, and this is what we found, and I think even these negative papers, when you don't have any new adverse event, are very important, because it gives people, I think, a reason to be more confident that the vaccines are safe. They're not worried that we're hiding something, everything is out there, and that if there is something there, we're going to find it and it's going to appear.

We've had a couple of these papers published in *JAMA*. The one on the

pneumococcal vaccine was published in *JAMA* just a couple of months ago, and the one that we did on varicella vaccine was published in *JAMA*, and other ones have been published in *Pediatrics*, *Pediatric Infectious Diseases*, and in other places -- these reports are in the literature.

And also, the other thing these papers do is encourage people to report, because I've heard people, I've heard physicians say that, oh, you just send in this report, but it goes into a black hole. They have no idea whether anybody looks at it. If you write a report that appears in a medical journal, then people do know that you look at these reports, and I think they're more apt, if they see something interesting that happens after a vaccine, they're more likely to report it. I can't document that, but it seems logical.

JS: By the way, the law does or does not compel the manufacturer to submit these . . .

SE: The manufacturers are required to submit reports of events they become aware of. So if somebody sends a report to the manufacturer, they have to send it to us. Or if there's a literature report that they become aware of, they have to send it to us.

JS: But there's no law compelling the harvesting of these, any adverse events.

SE: No, no. They don't have to go and look for them.

Now, sometimes they do marketing stuff. They're calling people to see if they're using this or that, and then somebody might tell them about something that happened. Then they have to report that.

There is a requirement through the National Childhood Vaccine Injury Act that health care providers actually have to report certain kinds of events that happen after certain vaccines. It's a very small subset of events, very serious -- deaths and a couple of other kinds of things that have been thought to possibly be associated with vaccines. Health care providers are actually required by law to report those, but there's no enforcement provision in the law. I've never heard of anybody getting in trouble for not reporting.

JS: But that doesn't, this doesn't cover sort of routine, you know, injection-site problems. It's more serious.

SE: No. There's something called a Vaccine Injury Table, and if you look at that, any particular event that's on that table in connection with a particular vaccine, the event-vaccine combination, if that occurs, it has to be reported.

I know from what Suzanne said that you had wanted to talk a little bit about what's happened with Biologics over the last couple of years. But I really do need to finish up for now.

Maybe we can do a follow-up. I can give you a few thoughts now. I don't have oodles and oodles to say about it.

JS: Well, in any case, we certainly would welcome any comments you'd like to convey about the . . . I mean, the transition that Biologics has gone through in the last few years, I'm sure the staff has reacted in many different ways to it. But we certainly

would like to get your input on what the changes in Biologics have been and what impact that has had on the Center itself.

SE: Well, it's a very difficult thing. I've sort of lived my life recognizing that there's always people who know more about any given thing than I do or know things that I don't know, and so it makes it hard to be too adamant about what's the right thing to do and what's the wrong thing to do. If somebody makes a decision that you disagree with, there's something inside you that says, what do they know that I don't know, that if I did know that, maybe I would feel differently?

But the announcement, the transition and the move of some of Biologics into Drugs certainly hit the Center very, very hard. Everybody I knew was shocked by the announcement and by the certainty, the definitiveness with which it was stated that this was not something that was being floated, this was not something where there was any discussion, apparently; this was something that was just a done deal and that was it. It was going to happen, and that was that. If you work for a pharmaceutical company, you know that kind of thing can happen. Your life changes overnight. There's a merger, there's a buyout, there's something. But you don't really expect it to happen in the government. It was, I mean, I will tell you that for the probably a good three or four months after that announcement, I didn't sleep through the night one time. I was very emotionally distressed.

I have a lot of close colleagues and friends in the Center for Drugs. I don't have any inherent hatred for the Center for Drugs or negative feelings. I think I worked very effectively with Janet Woodcock when she was at CBER and was sorry to see her leave

and go to CDER. I'd known her for many years before I came to FDA.

One of my closest colleagues in the time that I've been at FDA has been Bob Temple, and we're family friends and have been for many years before, and I expect we'll continue to be for many years after.

But it was just a real shock, and it was particularly a shock in the way it was done in that there didn't seem to have been given any real thought to what it was going to mean for some of the people at the FDA that the FDA should have really wanted to keep. Jay Siegel is the first name that comes to my mind.

I just think the world of Jay, and he's the kind of person who everybody knew could go out and make zillions of dollars if he wanted to outside, but he was very, very dedicated to public service. He was coming to the end of his twenty years in the Commissioned Corps, and I'd had discussions with him. He was debating about whether he should take his pension and go off and make those gazillions of dollars or whether he would want to stay at the FDA. He had pretty much come around to the view that he really loved what he was doing at the FDA and was going to stay at the FDA.

And then this announcement came. That was what I found, I think, of all the things, found so unimaginable that here they've got somebody -- they will never have somebody at the FDA smarter and more dedicated than Jay. I mean, he's just a fabulous, fabulous person, and yet they did this in a way that was guaranteed that he would leave. They took away his job.

JS: Why do you think it happened, and why do you think it happened the way it did?

SE: I really do not know. I do not know. Lots of different people have lots of different opinions.

The first thing a lot of people talked about was the ImClone mess, with that cancer drug where there was controversy about because it was CBER's drug and we refused to file the application because the application was flawed. That led to a lot of controversy. It's why Martha Stewart's in jail. People sold their stock at the last minute. There was a congressional hearing, and I feel CBER was treated very, very badly there. The CDER oncologist got up there and said that if he'd been in charge of it, this wouldn't have happened, which was nonsense. It isn't as though they'd never refused to file a product. This has happened now two and a half years, three years in the past, and so on. But it was infuriating that the CBER people were kind of left to twist in the wind, and there was no defense on this. So some people thought, well, that had something to do with it. The wrong people lost some money and were angry and needed to have something fixed.

Some people thought it had something to do with generic biologics, which Jay and Kathy Zoon were opposed to for some very good reasons, and that there were somehow powers-that-be who were determined that there would be generic biologics and thought this was . . . I don't know.

The reasons that were given never made any sense to any of us who knew anything about it. They said, well, we're going to make things more consistent. Well, there was lots of consistency. Believe me, there was much more consistency between regulatory policies for the same disease areas between CBER and CDER than there was in regulatory policies between different disease areas within CDER. We all went to the

same advisory committees. So that didn't ring true.

None of the arguments that were made rang true, really. It smacked of a political decision, but nobody really knew why they did it.

For some of us, for the people who worked on the products that were transferred, they moved from one place to another. They weren't particularly happy about it. For somebody like Jay, he had built up a very strong group, and then it was basically taken away from him. So he had no job. For someone like me, I had spent a lot of time building up groups, both statistics and epidemiology, to work with these products, and half my job was taken away. So it was disturbing.

JS: To what extent were you in touch with Jay Siegel and Kathy Zoon when this happened?

SE: We were all in touch with each other.

JS: What was their reaction? How did they . . .

SE: They were very upset, they were very upset. Jay was just devastated. Now, Jay has recovered very nicely. He's president of a pharmaceutical company and doing very well. I do see him from time to time. I expect to see him more since he's living in Philadelphia now, and I'm about to move there. I've never asked him the question whether, in retrospect now, is he glad this happened, because it meant he moved out and did something else. I have a hard time thinking that he will ever say he's glad it

happened, because he was so miserable. But he's doing, you know, he's doing very well, and I just think it's a shame that the FDA has lost a shining star like that. We have very few shining stars, and he was definitely one.

JS: And Kathy Zoon, of course, has moved on.

SE: And Kathy has moved on also.

I don't know what kind of interaction Kathy has had with the Office of the Commissioner. I think Kathy got along very well with Jane Henney. I know that there was flak with Mike Friedman. But she was director for ten years, and I don't know very much about a lot of the kinds of things that a commissioner, deputy commissioner, the budgetary kinds of things, those kinds of decisions. I know there have always been issues about how much research FDA should be supporting. CBER has a strong research program. That could be part of it, you know, sort of one way to reduce the amount of funds that are spent on research.

I don't know whether I'll ever know. Jay says he still doesn't know. He's out there in industry. We had a lot of people come running to us and tell us, "Oh, we think it's a terrible idea. We didn't tell anybody to do this." But industry, you know, they're going to tell whoever might have some regulatory authority what they want to hear. They don't want to make anybody angry.

JS: Research is a recognized function in the Center for Biologics and other centers. Can you compare the two? Is it more important to have research as a function of

Biologics than other centers, considering what Biologics does? How do you think that's perceived within the agency, especially within the Commissioner's office? Or how's that been perceived?

SE: You know, it's just too far away from what I do. The argument has been that CBER has always, in the therapeutics area in particular, managed cutting-edge products, and the feeling is you can't do an adequate job of regulating them unless you're really involved in the research as well, because things just move too fast and you'll be behind the eight ball. That argument makes some sense, but it doesn't make, has never made total sense to me because, after all, we don't have research programs in the area of every product that we regulate. So if that's the argument that you're resting it on, it's saying, well, we do a much better job of regulating these products where we have a research program, and maybe we don't do such a good job regulating these products where we don't have a research program. You know, that's hard for me to say, the extent to which laboratory research programs are needed. But I think some of the kinds of things that have come up the last few years, you know, problems where, if you have laboratory capability where you can actually get in there and try and do something about the problem, it seems to make sense. Certainly from the point of view of what I do, statistics and epidemiology, we need to have the kind of people who can be involved in research and are involved in research, or they're not going to really understand the kind of arguments that come back. The drug companies hire some very top-notch statisticians, and they also get consulting from academic statisticians, and if they come forward with an innovative kind of analysis, I need to have the kind of people on my staff who can

make judgments about whether that is a reasonable thing to do or not.

Now, my director of my Division of Biostatistics, who I was extremely fortunate in hiring, is somebody who had a long and very distinguished and productive career in academia before he came to work at FDA. He'd been on the advisory committees and had been doing a lot of consulting, when he and I knew each other. When this job came up, he decided that maybe it would be interesting to spend more time doing this work than continuing to churn out graduate students and teach courses, and it was very fortunate for FDA. It is hard to get those kinds of people to come when you don't give them some time for their own research.

Now, he's had a career in research. He's somebody who's going to do the research whether you give him time or not because he's going to work a sixty-hour week and he's going to be thinking at home and he's going to be working on the weekend and he's going to be doing those things. But not everybody wants to do that, and most statisticians in most places, even applied places, the understanding is that you have a day a week to work on your own stuff, and that has just never been the case at FDA, and it's too bad.

END OF INTERVIEW