History

of the

U. S. Food and Drug Administration

Interviewee: James Weixel

Interviewer: Ronald T. Ottes

Date: August 11, 1993

Place: Rockville, Md.

INTRODUCTION

This is a transcript of a taped oral history interview, one of a series conducted by the Food and Drug Administrations History Office. The interviews are with persons, whose recollections may serve to augment the written record. It is hoped that these narratives of things past will serve as one source along with written and pictorial source materials, for present and future researchers. The tapes and transcripts are a part of the collection of the National Library of Medicine.

TAPE INDEX SHEET

CASSETTE NUMBER(S) 1,2,3

GENERAL TOPIC OF INTERVIEW: History of the Food and Drug Administration

DATE: Aug. 11,1993 PLACE: Rockville, Md LENGTH: 135 minutes

INTERVIEWEE	INTERVIEWER
NAME: James Weixel	NAME:
ADDRESS: [redacted]	ADDRESS: Ronald T. Ottes
[redacted]	Food and Drug Adm.

FDA SERVICE DATES: FROM 1964 TO: 1993 RETIRED? Yes

TITLE: Consumer Safety Officer, Office of Health Affairs
(If retired, title of last FDA position)

CASS. NO.	SIDE NO.	EST. MIN. ON TAPE	PAGE NO.	SUBJECT
1	A	0	1	Introduction, Weixel background and education
		5	2	Early work experiences
		9	3	Joins FDA Philadelphia district
		11	4	Transfers to FDA headquarters-Drug registration
		17	6	Bob Porter
		20	7	Frank Fisket
		22	8	FDA reorganization and reassignments
		25	9	CPEHS
		26	9	EDRO, program planning and evaluation
		28	10	Field program performance evaluations
		29	10	Drug Listing
1	B	0	11	Project managers project reviews
		3	11	Product Codes
		5	12	Paul Hile, Sam Fine
		6	12	Government Wide Quality Assurance Program
		8	13	Office of Health Affairs
		9	13	Part 16 Hearings
		10	14	Chymopapain-Lyman Smith
		12	15	Reinstatement procedures for Clinical Investigator
		14	16	Clinical Investigator provisional reinstatement
		20	18	Human subject protection
		21	18	Institutional Review Boards
		22	18	Office of Health Affairs organization
		23	19	International Affairs Staff
		25	20	Harmonize International drug study requirements

CASS. NO.	SIDE NO.	EST. MIN. ON TAPE	PAGE NO.	SUBJECT
2	A	0	21	Medical Affairs Staff
		2	22	Community research-Drugs for HIV infections
		5	23	Compassionate IND's
		7	24	Health Assessment Policy Staff
		7	24	Drug patent term extensions
		8	24	FDA's IRB's Research in Human Subjects Cmte (RIHSC)
		10	25	Controlled Drugs-FDA,DEA,NIDA,WHO
		13	26	Alternative therapy
		16	27	American ASS'n of Tissue Banks voluntary standards
		21	29	Umbilical cord grafts
		22	29	Corneal lenticules
		23	29	Creutzfeld-Jacob disease
		25	30	Porcine heart valve
		28	30	FDA regulation of tissue and sperm banks
2	B	0	31	Congressional interest in tissue and sperm bank regulations
		4	32	National Organ Transplant Act of 1984
		6	32	Organ procurement and transplant network
		8	33	Organ donor screening and testing
		9	33	Eye Bank Ass'n of America
		11	34	Sperm Bank requirements-various states
		17	36	Requirements of Federal Government?
		19	37	User Fees
		22	38	Cell cultures-Somatic Cell therapy
		24	39	Role of Office of Health Affairs under various Commissioners
		27	41	Silicone breast implants
3	A	0	41	Silicone breast implants continued
		2	42	Edward's committee review of FDA's Advisory committees
		9	44	Review of DESI denials
		12	45	Product Recall classifications
		15	46	Wrap-up
		16	47	End of interview

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James A. Weixel

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Chief, History of Medicine Division
National Library of Medicine

RO: This interview is one of a series of oral interviews on the history of the Food and Drug Administration. Today we are interviewing James Weixel, a retired FDA employee, in the Parklawn Building, Rockville, Maryland. The date is August 11, 1993. I am Ronald Ottes. This interview will be placed in the National Library of Medicine and become a part of the Food and Drug Administration's oral history program.

Jim, to start this interview, would you briefly sketch where and when you were born, your education, your experience, if any, prior to coming to FDA, and what brought you to FDA. And then as we follow your career in FDA I'd kind of like to go into some of the interesting projects or programs that you were involved in.

JW: I was born May 7, 1928, in Pittsburgh, Pennsylvania, and grew up there on the north side of Pittsburgh, where I attended elementary and high school there, and then went to the University of Pittsburgh where I graduated in 1950 with a Bachelor of Science in Zoology.

At that time it was during the Korean War, and I had applied for admission to medical school, and Pitt had something like 2,500 applicants for every one of about eighty-three to eighty-five positions in the freshman class. So I was literally stalling around waiting to see whether or not I could get into medical school, and in the interim took a job as an operating room technician at Saint Francis Hospital in Pittsburgh and became familiar with the jargon of medicine and surgery and learned a lot about surgical procedures, having seen hundreds of operations and "scrubbed-in" on most of them.

So then I went in the army and served two years during the Korean War and spent part of that time as a medical lab technician at Fort McClellan in Alabama and then as a food lab technician in Tokyo. After I got out of the service I took a job with Parke-Davis for a number of years as a pharmaceutical salesman with a territory there in Pittsburgh.

Then subsequent to that, to the time when I joined--it was several years later--I ran into another salesman that I had become acquainted with, who represented a different company. He had worked for Merck for a while and one of the other pharmaceutical firms. And I met him at a hospital in Pittsburgh, just encountered him by chance, and asked him how he was doing, and he said he was leaving pharmaceutical sales to take a job with FDA.

And I, you know, as incredible as it sounds now, wasn't even aware of FDA. This was about 1963, I guess. So I said, "What in the hell is FDA?" So he went on to explain what he'd be doing, and he was going to join Buffalo district as an inspector. Buffalo at that time had a small resident post in Pittsburgh. And he was telling me how he was going to be going out on these two-weeks road trips doing feed mills, and you know, getting pesticide samples, and inspecting food and drug firms, and so on. (Laughter) I didn't think much more about it.

RO: Who was that, Jim? Do you remember?

JW: Yes. His name was Joe Brochetti. And so Joe took a job with FDA in Buffalo. He and his wife and four kids moved up there, and it turned out that she was a little homesick for Pittsburgh and he did leave. But oddly enough, he went with a different type of pharmaceutical firm and he got into experimental therapeutics and became a representative for them in dealing with clinical investigators and stayed with that job for decades, I guess, and then retired a few years ago.

But, you know, I kept that in the back of my mind, and later on I got a little greedy and I left Parke-Davis for another drug firm that offered more money but was also much more aggressive in its sales policies. After about a year and a half I got fired for not closing forcefully enough in the doctor's office. They felt that you should not only present the information to them, but should get scout's honor that he was going to use the stuff, and then come back a month later and see whether he kept his promise. So this regional manager . . . My district manager had high praise

for me, but the regional manager from Chicago came in and worked with me for one day, (Laughter) and the impression I made on him was so negative that he insisted that my district manager fire me.

So reluctantly he did that and I was thinking, as I was coming back from an exhibit that this pharmaceutical company had presented in one of the hotels in Pittsburgh, as I walked past the Grant Building, which was where FDA's little resident post was located. I thought, "Gee, you know, Joe Brochetti told me about that. Well, I'm going to go in." And Ted Loveridge just happened to be there that day and another wonderful guy who headed that resident post and then went to the Bureau of Foods later on. His name escapes me right now. But he was more or less the chief resident there. So I talked to Ted, and he said, "Oh, yes, you just take a test," and he arranged for that. (Laughter)

So I took the test and a few weeks later Fermer Adair called me on the phone and said, "You know, I'm making a swing through western Pennsylvania doing some recruiting, and I'd like to interview you." So I said, "Sure." I met him at a motel in Coraopolis where he was staying, probably within the thirteen-dollar-a-day per diem (Laughter) that we had then. And so he interviewed me, and he said, "Well, you can have a job at FDA. You can come to either Baltimore, Philadelphia, or Buffalo." He said, "I'm authorized to recruit for all three." I thought about it for a minute, and you know, there was more of a drug industry in Philadelphia, and also it was the only one of the three that had one-week road trips. And of course, I had a wife and two kids, and I thought that one-week road trip has decided advantages. I don't need to be taking two-week road trips down in the Carolinas doing canneries. I can do canneries in South Jersey and come home at night. So I said, "Philadelphia."

Well, it worked out pretty well. And then by sheer coincidence Jim Greene who was my chief inspector came out to the inspector's room one day . . .

RO: What year was this, Jim?

JW: This was 19-- . . . By this time it was late 1964. I joined Philadelphia district in May of 1964, and Fred Lofsvold swore me in. Jim came out, and he was just socializing one day and said, "What would you like to do?" And I had heard, or read in some of the publications that crossed my desk, about "Food and Drug Officers." And as little as I knew about it, it seemed to suggest to me the kind of activity that might be relevant to my background, both in the army and in the O.R. and in the years of drug sales. So I just said, "Well, it might be nice to become a Food and Drug Officer sometime. And Jim just filed that away, I guess.

And Harris Kenyon was talking to him on the phone a month or two later and bemoaning the fact that a fellow who had come down from Philadelphia District a year or two previously to take over drug registration--which was an obligation that had come to FDA under the 1962 amendments--was leaving to pursue a master's degree in business administration or something. And Jim Greene said, "You know, there's a guy on my staff that would like to get into administration." And he said, "Do you think you could take him on a detail and see whether or not he'll work out, or if he likes you." And Harris said, "Yes, all right." So they worked out a thirty-day detail. Jim Greene came out and asked me if I wanted to do it, and I said, "Sure, I'll try."

So FDA was then headquartered in Federal Building 8 at Third and C in the District. So I took that thirty-day detail, and I worked with Frank Thompson, who had been recruited . . . Frank was a GS-13 working at headquarters and had been recruited to take over the Drug Registration Office. At that time it was a small office; there was just one professional and a clerk and sometimes maybe a second clerk part time. But coincidentally, the Drug Abuse Control Amendments of 1965 had just been passed, so actually this was . . . I guess when Jim Greene and I had talked it was late 1965. And this, then, was after January 1, 1966.

FDA had the obligation of registering all these establishments that had never been required to register before. These were simply warehouses that handled controlled drugs but didn't manufacture, repack, or relabel anything. So there was

all sorts of confusion about who had to register and who didn't, who might be exempt, and all this sort of thing, and many disputes. If an inspector from a field office went in and said, "Look, now you are obligated to register," they would write and dispute that, and we'd have to write back to them. So there was an enormous workload all of a sudden. It became a much more complicated operation than it had been for the few years that it had been in existence prior to that.

RO: Where was this office situated? The Bureau of . . .

JW: This was probably . . . It was part of old BRC--the Bureau of Regulatory Compliance. So I worked at that detail there, and Frank Thompson recommended to Harris Kenyon that he hire me. And so they offered me the job, and I moved my family down there, actually in early March, because our younger son was born just a couple of weeks after we got there, and his birthday is March 20. So we had moved in, I guess, about the first of March.

RO: When you came in at Philadelphia, what grade did you come in at?

JW: As a GS-5. And in those days, you only had to spend six months as a 5 before becoming a 7. So this worked out very well for me. I got my 9 to go to D.C. to take over that registration office. I no sooner got off the elevator than they reorganized. (Laughter) I was transferred to Washington to take a job; fortunately the job didn't disappear. Harris Kenyon was given a slightly different operation. I'm not sure of the time relationships, but he became the assistant commissioner for field administration or something like that. And he didn't want a staff. He wanted to keep it small as much as possible and just kind of report to Ken Kirk, and you know, sort of run it out of his hip pocket and hope nothing went wrong.

RO: Well, then, you and Frank Thompson were together there . . .

JW: Well, Frank went back to his other job. And I was in drug registration by myself with one clerk.

RO: I see.

JW: So it was a good experience. I mean, I got a lot of experience in reading and responding to correspondence, and I got it most in those aspects of the FD&C Act that related to the Drug Abuse Control Amendments of '65 and having to interpret them. And fortunately, Doug Hansen, who took over what became a division within BRC hadn't had a lot of exposure to this stuff, and he was happy to have anybody that understood it and could carry on this correspondence. So I got my 11 the following year, and my 12 about a little over eleven months after that. So I had gone from a 5 to a 12 in a little less than four years.

And then Ken Kirk, bless his heart, put a freeze on promotions, and I was delayed a few months in getting my 13, but I got the 13 the following August. So I really couldn't complain; I'd gone from a 5 to a 13 in five years and four months. So that probably set some kind of a record then, although Phil White and any number of others certainly got to be 14s and 15s, and it took me a few more years to get a 14 and I never got beyond that. But it was really rewarding, and we got a catch-up raise of about 10 percent just at the time I got my 13--all federal employees received the "catch-up" raise. So here I was going from a 12 to a 13 plus a 10 percent increase in a 13 salary, and that seemed glorious.

But one thing I haven't mentioned up until now that really was one of the most fortunate things in my career was that when the reorganization I mentioned took place, I was assigned to Bob Porter, and he took over that group. Drug Registration was just one of the units that he regulated. And Frank Thompson was telling me what to expect, you know. Here I am an utter stranger caught in this reorganization with no idea of where I'm going to wind up or who I'll be working for. And Frank said to me, "You know, you're really lucky. You're going to work for one

of the nicest guys in FDA," and that's the way it turned out to be. Bob certainly was one of the nicest guys I ever encountered in or out of government and gifted in many ways.

I've often thought that one of the deficits in FDA in more recent years has been the absence of anything like a mentor, you know, a true mentor that we were fortunate enough to have in those days. I mean, Bob Porter was one and many, many others in district offices: district directors and branch chiefs and things like that who truly did function as mentors. I think that's a big loss. The absence of those in today's FDA I think is a considerable loss.

RO: Well, don't you think, Jim, a lot of it was the fact that then it was . . . You know, like some people said, you didn't work for the Food and Drug Administration, you were a part of it. And don't you think a lot of it was that attitude?

JW: Oh yes. And these guys who had been around and had done a little bit of everything, as Bob had done in New Mexico and Utah and places like that, and worked first-hand with U.S. Attorneys, and cajoled them, and gotten them to pursue cases that they might have otherwise slept through . . . You know, these FDA guys really were involved.

We had a man in Philadelphia who was one of the supervisors there, Frank Fisket. And Frank was like a big dog. Everybody liked Frank. His idea of supervision was to take the stuff from his "out" box and put it in George Gerstenberg's "in" box. George was the other supervisor, and seemed to emjoy Frank. We just enjoyed Frank's good humor and exuberance and stuff like that. But he was another one who had, you know, given of himself unselfishly when he was in Wisconsin or in Minnesota District, and they would monitor illegal operations in the food industry and stay up all night to try and catch somebody shipping adulterated food--this sort of thing. So some of that rubs off on new employees. For me there was just a lot of coincidence--very fortunate stuff.

RO: You were at the right place.

JW: I was at the right place at the right time. And so then I ran into Keith Dawson one time. Keith was going to what was affectionately known as "charm school" course, the executive development program, and that left an opening in Bob Porter's group. I neglected to mention that there was another reorganization along the way that transferred me to Pete Finkel's office. Pete was a GS-15 branch chief that handled a lot of statistical aspects, some of what is now back in Keith Dawson's group in the planning and evaluation and that sort of thing. Bob Porter was separated out from that, and so Keith stayed with Porter, and I wound up with Carmen Soviero and Pete Finkel. Keith told me that his going to executive development school meant that there was an opening in Bob Porter's group and asked if I had any interest since I had worked with those people previously as a member of Bob's staff. I said, "Oh, definitely." So I got in there. And then later on when Keith came back from executive development school and Bob Porter transferred to Denver, Keith was promoted to Porter's job, and I was promoted to Keith's job.

RO: Now, wait a while, Jim. When did you leave drug registration? Was that with the reorganization when the Bureau of Drugs was formed?

JW: No, the Bureau of Drugs didn't get drug registration until many years later. A man named Ralph Lee took over drug registration as I left. Ralph had worked for Bob Porter as a statistical clerk, as a GS-7 or maybe a 9 statistical clerk. There was great difficulty in getting Ralph an 11 in drug registration, although that finally happened. Then later on they transferred drug registration to what was then the Bureau of Drugs.

RO: I see, OK.

JW: You know, in one of the subsequent reorganizations.

RO: Well that, then, brought you to what was later known as the executive director of regional operations.

JW: Yes. And just at about that time, I guess, Harris Kenyon left or became a regional associate commissioner. They had these RACs out in . . .

RO: Well, you know, he left when CPEHS was formed.

JW: OK. And Doug Hansen became one of the RACs in Seattle region. And Sam Fine took over what was a little more mature, sophisticated version of what Harris Kenyon had had. And Paul Hile, as you very well know, had been the project manager on a contract with Booz Allen and was looking for honest work, and he wound up as Sam's deputy (Laughter) and prospered no end. So we had fun working for Paul and for Bob Porter. Porter had planning and evaluation, and I ended up in evaluation, and Sterk Larson had the comparable job in planning.

That stint was helpful. I learned a lot about compliance programs, their issuance, their development, what goes into them. In those days there were multiple parts, and you had contributions from Hy Eiduson and his group who had laboratory science as their concern. And you had compliance components, and then the basic elements of the program itself as defined by specialists in foods or drugs or whatever it related to, vet medicine. The application of resources and the distribution of resources within FDA was something entirely new to me.

We had used punch cards in the old days. When you'd come back from an inspection you'd dash off a little card that said what category of an inspection it was, and what the operation was, whether it was an establishment visit or inspection and whether it was for surveillance or compliance or whatever. But this system became much more involved. The planning process got more complicated and more explicit,

and evaluating field performance became a little more detailed. And our section got involved in reading the printouts that related to field performance to see how the field was performing with respect to the plan--how closely they were following the overall plan, and what they were doing in each area, and keeping track of the resources that were being expended, because sometimes for reasons of emergency situations or something like the intensified drug inspection program, enormous quantities of resource would be expended in a way that was unanticipated.

RO: Did you do this overall field, or region by district, or . . .

JW: We did it by district and overall field, because the budget allotted so much food time to the field to be broken out according to establishment inventory by district. And so we would look at the district's performance vis-à-vis its obligations, and then also look at the overall field consumption of resources to see whether or not they were spending 20 percent more in foods than had ever been anticipated or whether drugs was gobbling it all up and foods were being shortchanged.

RO: While you were there did you have a chance to look at maybe other programs that you thought the agency should be in, or did you just do whatever the bureaus had sent down to . . .

JW: Well, we had other things that we thought they should be involved in. In fact, Paul Hile, while I was working for him through Bob Porter, and I had some go-arounds with the Bureau of Drugs trying to get them to use drug listing files, trying to create a drug listing file. They used an awful lot of field personnel to go out and gather information from drug firms, and they hadn't planned ahead and didn't really know how to handle the information when it came in. They got some casual employees and some temporaries that their manager, Herb Behrens, had enormous difficulty in working with. Herb I think did an excellent job under extremely difficult

circumstances--because they gave him a bunch of malcontents and some real characters--to try and sift through these printouts that the field had dutifully put together and sent in in an effort to find out what products companies were making and get a complete and accurate list.

The data base became just a hopeless mess that was inaccessible by anybody. So we worked with them to try and get that thing in a more reasonable format. Even though it went on for years and years and years, there were still problems with it and problems with inability to contrast that drug inventory information with the NDA files and see whether or not NDAs existed for all the drugs that should have them and things like that.

(Interruption)

JW: Both Dr. Edwards and Dr. Schmidt utilized a practice that involved project management. They took more or less the inventory of agency obligations and broke them out into different codes, distinct codes, that the field and others applied to them. Some would be in drugs, some in foods, some in veterinary medicine. It was . . . The entire spectrum of agency obligations were broken up into discreet projects and each would have its own manager. Then they would have these project reviews at the commissioner's weekly staff meetings. They would schedule the review of perhaps one program each week. So I represented the office of planning and analysis on those that related to drugs and biologics, and somebody else was handling foods and devices and things like that. That was very interesting.

Then we got involved in an infamous "product code" (Laughter) that was the chagrin and exasperation of the field force, I guess, but was felt to be necessary in order to keep track of what was going on: what products were being inspected, and what package sizes were being inspected, and as much as possible differentiating among products and among industries. So one of the fellows who worked for me just about devoted his life to that--a man named Warren Howard. He had incredible

patience and perseverance in working on something that had no advocate other than us (Laughter) and got scant cooperation, or at least got diverse views about how it should go from the specialists in the centers, like Foods, and Drugs, and so on, and then also from the field. Fortunately, Warren had been an inspector in Kansas City district and in Philadelphia and understood how this would have to be applied by what we called inspectors then that are investigators now. That perhaps made it a little easier, although he still got a lot of hostility for that.

Then I had the opportunity to take a detail in the Office of Health Affairs in about March of 1980. Bob Spencer, who . . . Shoot, I left out a whole four years there. I went to the Air Force Academy to participate in a program training supervisors, and I was talking to them about the data processing, something about the program-oriented data system, and also how program evaluation worked at headquarters. I was out there for a week with Paul Hile, and by this time Paul had succeeded Sam Fine. Sam Fine had gone from what was the forerunner to EDRO to take Ken Kirk's job when Ken Kirk retired as associate commissioner for compliance. Paul moved up from deputy to the executive director of regional operations when Sam left to become associate commissioner for compliance. So Sam retired and Paul then became associate commissioner for compliance. And he said to me . . . You know, he was talking to me about going to work perhaps for one of the units that he had.

Shortly after that, Frank Flaherty--who had the government-wide quality assurance program which had just been inaugurated in 1975 and perhaps preliminarily in late 1974--asked me if I wanted a job as a supervisor in that group. And so I thought, yes, I'd try that. So I took over the drug group in Frank's office and worked there from 1976 to 1980. We assisted the armed forces, the Veteran's Administration, and Public Health Service in procuring medical products of acceptable quality. Then in 1980 I had this opportunity for a detail in the Office of Health Affairs, and I took that.

After the detail they offered me a permanent position; so in May of 1980 I joined the staff in Health Affairs as a permanent party and remained there until I retired on June 3, 1993. That provided a lot of interesting opportunities. One of the first things I became involved in was a Part 16 Hearing for a clinical investigator. I had never been involved in anything like this before. This was a physician that the Bureau of Drugs felt should be disqualified for conduct that had taken place while he was serving as a clinical investigator on certain drugs which happened to be antihypertensive.

RO: Now, this Part 16, when those charges are made against a clinical investigator, they have the right to a hearing? Is that . . .

JW: Yes. When those charges are made against a clinical investigator they're offered an informal hearing. If they accept that and they then satisfy the bureau that their conduct was really justifiable under the circumstances, and that there had been a misunderstanding, and there really was nothing potentially injurious in what they had done, then it can end there. But if their explanation is not entirely satisfactory, then the bureau can proceed and can offer them a Part 16 hearing, a public evidentiary hearing that would allow them to sort of defend themselves. And they can bring counsel with them if they want to, and that's what happened in this case.

RO: Who holds those hearings?

JW: The Office of Health Affairs had been delegated responsibility to provide the presiding officer. So at that time, Stuart Nightingale, who had succeeded Mark Novitch, as acting associate commissioner for Health Affairs, served as the presiding officer. Mark Novitch had moved up to deputy commissioner at that time. Stuart, then, who had been a deputy associate commissioner for medicine within Mark Novitch's Office of Health Affairs moved up to the chief slot and the other one was

sort of abolished, although I held it for a year or so on an acting basis even though I wasn't a physician.

But Stuart served as presiding officer, and the clinical investigator and his two attorneys presented their side and then the bureau presented its side. Then we were involved in preparing a report of that hearing and making a recommendation to the commissioner, and we worked with the HEW/FDA general counsel. We had our attorney, and the bureau had their attorney, and of course, the clinical investigator had his attorneys that he brought from outside the agency. So that got me started on that.

Then when I was an acting supervisor in that office I oversaw the conduct of about four or five more disqualifications for clinical investigators. Sometimes the clinical investigator was disqualified; sometimes he ends up signing a consent agreement to restrict his participation and so on.

RO: Was he submitting fraudulent reports or . . .

JW: Well, there can be all kinds of violations, but often it is in one way or another submitting fraudulent reports. Sometimes it's inadvertent; sometimes it's deliberate. But in this case there were some electrocardiograms and I believe some x-rays of one patient that were submitted with another patient's name, and some sloppy record-keeping, and test results that weren't accurate, and things like that. There are any number of improprieties that can be involved in a bureau's conclusion that a clinical investigator should be disqualified. But basically they violate some aspect of regulations that pertain to clinical investigation and the obligations of investigators.

Then we encountered a previously disqualified investigator who wanted to be reinstated for the purpose of conducting a clinical investigation. This was kind of an interesting thing, because it was a physician named Lyman Smith who had sort of pioneered the use of chymopapain as a substitute for surgery in the management of ruptured intervertebral disks. He had been disqualified for stepping outside the

protocol when he was doing clinical investigations with chymopapain several years earlier in the 1970s. He had treated a patient and not bothered to record it. The patient wasn't part of the study and things like this. So he ended up being disqualified, and he wanted to come back in.

So I then worked with the Bureau of Drugs, and with general counsel, and with Ernie Brisson in what was still probably EDRO to come up with reinstatement proceedings, which we published in about September of 1982 in the *Federal Register*, not as regulations but as guidelines for the reinstatement of a clinical investigator. We proceeded to make certain demands upon Dr. Smith before he would be given a provisional reinstatement. And the way we wrote the reinstatement procedures, a clinical investigator has to come in with assurances that he will not commit the violations for which he was disqualified. To some extent FDA is stuck with what's written in the regulations. Our own regulations say that a clinical investigator can be disqualified, but if that clinical investigator gives adequate assurances that the violations will be remedied, not repeated, that FDA is obligated to let them function as clinical investigators again. So all FDA can do is be very demanding about the adequacy about those assurances, and we try to do that and insist that somebody look over their shoulder.

So what happened was there were two members of the hospital staff that had to sign agreements that if Dr. Smith was allowed to use chymopapain again in an investigational study that it would only be available to him through the pharmacy, and that the pharmacist would attest to each dose that was provided to him and keep careful control over what he was permitted to have, and that another member of the hospital staff, a surgeon I believe, would verify that any patient he treated was part of the study and that the patient was being treated within the requirements of the protocol.

RO: Does FDA go out on-site and investigate these things that are being done, or do you take their word for it?

JW: Well the center can always . . . There have been so few of them, really. The only provisional reinstatement was the one for Lyman Smith back then, and he was allowed to go ahead and work with chymopapain again, and the drug, you know, fell into disrepute because of side effects that were produced--paralysis and some other serious deficiencies that were demonstrated clinically--and the practice was more or less abandoned.

But the bureau always has the option once a clinical investigator is given provisional reinstatement to see that his or her conduct is investigated. They can simply make it an assignment through the Bio-Mo managers program, which we probably don't have time to go into in detail, but it works . . . It's a collaborative effort involving the field and compliance officials at headquarters and the bureaus, or the centers now. They all get together and coordinate these assignments and their issuance. I think Paul LaPore does it in the Office of Regulatory Affairs now. But there's ample opportunity to check and see that this is being done. Actually if someone were to try and get permanent reinstatement, that's what would happen. There would be some verification that the study conducted during provisional reinstatement was done properly and all the rules were observed. In the Lyman Smith case, all he really wanted was to be involved in that chymopapain thing, because he and a nephew or something like that were involved in the company that was making it.

We had one other instance of a clinical investigator, a psychiatrist, who had been disqualified. And he tried several times to get reinstated, and he even had Dr. Herbert Ley come in and represent him at a meeting with Dr. Nightingale and some officials like Dr. Alan Lisook from the Bureau of Drugs and people like that, to discuss just what was necessary to get reinstated. And he submitted extensive assurances. They would have been acceptable, but the sponsors kept dropping out.

Sometimes when they found out that he had been disqualified and they had not known that previously, they dropped him. Sometimes it was just an economic thing, I guess, or the sponsors learned something, developed some adverse information about their own product and decided not to go forward with it. So every two or three years we'd hear from this clinical investigator who wanted to be reinstated, and he'd have another sponsor.

So Dr. . . . Oh, the commissioner who followed Jere Goyan.

RO: Dr. Hayes?

JW: Dr. Hayes. Commissioner Hayes did send him what we came to refer to as a shopping letter which said, "Your assurances are acceptable and if you can find . . . You are permitted to show this (letter from Dr. Hayes) to a prospective sponsor. And if you find one, you have to submit the protocol and submit any more assurances that we feel are necessary and particular to that protocol. And then you'll be granted permission to participate in one study. You'll be given a provisional reinstatement for the purpose of participating in that one study, after which if you want permanent reinstatement, you can request it and we'll look at the way that study was conducted, and the commissioner will make a decision at that time as to whether you can do it or not."

So a few months ago this doctor finally, on about the fifth attempt, did get a sponsor of what amounted to a seeding program almost. It wasn't that much of a scientific study. It involved literally thousands of psychiatrists, I think, treating a few patients, four or five patients apiece, with a drug that was already marketed for another purpose and they were looking at a different indication. So he was given provisional reinstatement for that, and will probably never come back and ask for permanent reinstatement, because I don't think he has any interest in functioning as a clinical investigator; he probably just wanted to get his name cleared for his own satisfaction.

RO: Sure.

JW: So those were interesting. Then I got involved to some extent in Health Affairs in human subject protection. FDA has the obligation to see that Parts 50 and 56 of our regulations are observed. Part 50 has to do with informed consent in clinical investigations, and Part 56 with the organization and conduct of Institutional Review Boards (IRBs). I participated in reviewing the development of IRB information sheets, and then in going out to workshops that were held jointly with NIH's Office of Protection from Research Risks and giving talks and participating in these workshops to acquaint institutional review boards with their obligations under the law.

RO: Let me ask you something here as far as the organization of the Office of Health Affairs. There's a Medicine staff, and then you were involved I think in the Health Assessment Policy staff.

JW: Right, right.

RO: What's the distinction?

JW: I'd like to describe the organization of Health Affairs, and then kind of get back to the thing that took up a lot of the last ten years that I worked on within Health Affairs. It's interesting now because of what's on the horizon.

But Health Affairs is composed of three staffs: one is the International Affairs staff; one is the Medicine staff; and one is the Health Assessment Policy staff. The International Affairs staff has some involvement in international travel for anybody in FDA. They deal with embassies, U.S. embassies in foreign countries, sending communications back and forth about things that need to be recalled or health hazards that might pertain to something that was shipped from a foreign

country to this country and from us to a foreign country. Then there are a couple major . . .

Well, and then visiting health officials from foreign countries communicate with that office, and the International Affairs staff would coordinate activities and help schedule interviews for them within FDA. They'd set interviews up in Drugs and in Devices, and we'd provide the foreign officials with copies of the *Federal Register*, copies of the CFR, and you know, get them around to different places and help them make the contacts that they needed among FDA's officials.

But one of the big things that they've been involved in in the last few years has to do with a project that has come to be known as the International Conference on Harmonizing Technical Requirements for Drug Approvals. In recent years trade has really blossomed, and this has become a big thing that FDA has gotten involved in even though it didn't want to. And there are some major concerns to FDA in this whole area. It's not just a question of enhancing the position of domestic industry or anything like that, but getting cooperation from foreign governments in the setting of standards that will eliminate the need for duplicative research in clinical investigation, and thereby perhaps help hold down the cost of pharmaceuticals, but more importantly, help develop international standards that are not deficient with respect to FDA's own rigorous standards. We don't want our products to be kept out of foreign countries because our standards are different than everybody else's. And we don't want to have to keep out the products of other countries simply because they don't meet our standards, because that's almost certain to be misinterpreted.

RO: So this means accepting the studies that have been done in other countries . . .

JW: To some extent.

RO: And getting them to accept the studies that have been done in the United States.

JW: Yes, and getting them to be truly comparable so that they can be accepted. And so FDA in Health Affairs has been working with representatives of the European community and Japan to work this stuff out. There was a conference in Brussels in '91, and then there will be another one in October of this year in, I think, Orlando, Florida. And these people will get together again and talk about ways to harmonize their requirements. The hope is that FDA won't get boxed into a position where we're so different from everybody else that we just can't send anything overseas or . . . We can't hinder . . . It will impair trade agreements that would ordinarily allow the freer interchange of merchandise.

RO: What about the inspections of these manufacturing plants over there? FDA still does that.

JW: Yes, FDA still does that, and they still . . . If their products are being offered, or if any clinical investigations are being offered in support of investigational exemptions in this country--like NDAs or PMAs for devices or something like that--FDA would certainly continue to inspect on the premises overseas.

RO: Do you think that they will ever get that we'll be willing to accept each other's inspections of these manufacturing plants?

JW: Perhaps. We do it with Switzerland. We've done it with them for many years, and I think there are some agreements with some of the Scandinavian countries--perhaps Sweden and somebody in addition to Switzerland. It would still almost have to be on a country-by-country basis.

RO: Well, sure.

JW: Because you couldn't assume that everybody would be as rigorous in their inspection procedures or that they would have compliance programs like we do or trained inspectors and stuff. So that may be in a way the easiest part of it to accomplish, but even that would have some adversity associated with it.

RO: Sure.

JW: Another important aspect of this is that one of FDA's biggest fears is that trade representatives of the United States--from the Department of Commerce or from wherever--will enter into negotiations with these other countries oblivious to the requirements and the statutes that we at FDA enforce. That could be a real horror story. So Health Affairs works with other U.S. agencies closely to keep them informed, and to be involved, to make sure that nobody's giving away the store.

(Interruption)

JW: The Medicine staff in Health Affairs is involved heavily in communicating with professional organizations--groups of physicians, pharmacists, people like that. The Medicine staff attends probably fifteen or twenty major professional meetings a year and exhibits at probably half a dozen.

RO: Exhibits? What do you mean?

JW: An FDA exhibit.

RO: Oh. What FDA is and does.

JW: Yes. And they also send information out on a regular basis to a mailing list, to a large mailing list. They'll communicate with groups of physicians--not just the AMA--with the American College of Ophthalmology or the American Academy of Pediatrics or some group that they have a message they want to get to, you know, they want to deliver to. They also . . . The director of the Medical Affairs staff will attend AMA functions and be there when they come up with their resolutions and their recommendations, some of which affect FDA almost every year, because of something that they're recommending that FDA regulates or that FDA will regulate, they recommend that FDA not do what it's doing in some other area, or . . . So you need that liaison to help explain FDA's position and articulate it in a way that is comprehensible by others and also does as much as possible to persuade them that it's a reasonable position.

And then the medical staff has been actively engaged in the area of drugs intended to treat HIV infection and the consequences of HIV infection, like AIDS itself and various infections that occur as a result of diminished immune response and stuff. There has been more and more what is called community research. FDA, through the Office of Health Affairs, has maintained liaison with these people in the AIDS area in order to be helpful to them, but also to prevent wasteful efforts. There's an awful lot of money and time being spent on this so-called community research, and if it is so unorthodoxed that you can't draw any statistical inferences from the results, then it's lost. And the proponents will be upset because nothing comes of it. They'll feel that they showed something, but if it's such sloppy work that it's not reproducible then FDA's not going to accept it; it can't be used in support of the marketing of a new drug or anything.

RO: Do they have to submit a protocol for this community research, or does it just happen?

JW: Well, sometimes I guess it just happens, and some of it they do submit protocols for. There are physicians . . . There's a group of physicians; they call themselves Physicians for Human Rights. They're interested particularly in AIDS, and FDA has worked with them. The Health Affairs has arranged programs for them to come in on a Saturday and get physicians from FDA's Division of Viral Products to explain to them what a protocol had to be like and why, and give them handouts on what FDA requires, and how it's not arbitrary. You know, it's necessary, and why it's necessary.

It really smoothed some troubled waters and gotten these people, increased the respect of these physicians for FDA and for FDA's reasonableness. Then they, the physicians, can go back and talk to patients with AIDS or HIV infection and assure them that what FDA's requiring is not unreasonable. Otherwise the patients will be stuck with anecdotal information they can't rely on, and they can waste a lot of time and money pursuing avenues of therapy that have no merit. So Health Affairs has been engaged in that pretty heavily in the last year or two, and in working with NIH and the public on concepts like treatment INDs and parallel track and things like that which can easily get out of hand and reduce the value of any information that's obtained from those things.

RO: How about compassionate INDs? Does Health Affairs get involved in . . .

JW: No, no, that's something that . . . Well, they may call Health Affairs, and Health Affairs will refer them to Dr. Temple's office or someplace in the Center for Drugs. Dr. Temple has mentioned at times that there really is no such thing, in his view, as a compassionate IND. He said, "An IND's an IND." And there are various circumstances under which one can be granted.

The reviewing division, if contacted by a physician who knows about the existence of a drug and has a patient he thinks is in dire circumstances and needs that drug, and if the company is willing to make it available under those special

conditions, the Center for Drugs can put the parties in contact with one another, put the primary care physician in contact with the drug firm and say that FDA has no objection to providing the drug as long as the treating physician feeds back some information, even though it's not exquisitely scientific--at least what happened, and what dose he gave, and for how long a period of time, and that kind of stuff. But there are some of the things I've been . . . Well, there are things that those two offices have been involved in.

Now Health Assessment Policy staff has responsibility for something that came along to FDA in recent years, and that's the patent term extension obligations. The centers are involved, like the Center for Drugs, in determining when an IND became effective and so on, but the Office of Health Affairs serves as sort of a dispassionate party in all this, gathering information from the Center for Drugs and working with the U.S. Patent Office and aiding the Patent Office in establishing the length of time that a patent term should be extended based on the circumstances that attend the way the drug company applied for it and how much time was spent in the IND phase and so on.

So that's been a principal activity for the Health Assessment Policy staff, and so has human subject protection--the development and dissemination of IRB information sheets and another package of sheets for clinical investigators acquainting them with their responsibilities, telling them what an inspection by FDA will consist of, and how to keep good records. There are about five areas that are covered by the clinical investigator inspection sheets and about twenty-two or twenty-three by the general IRB information sheets. FDA and the Office of Health Affairs' Health Assessment Policy staff continues to collaborate with NIH in putting on workshops regarding human subject protection and the obligations under the law.

Health Assessment Policy staff, working in conjunction with the Medicine staff in Health Affairs, oversees the operation and chairs the operation of FDA's own IRB, which is known as the RIHSC Committee--that's Research in Human Subjects Committee. They look at studies sponsored by FDA's Center for Drugs on

bioavailability or biologics, maybe for vaccines or something, to see that the subjects enrolled in the study are being given informed consent and that they're properly protected. So that's another aspect of that office.

Then Health Assessment Policy staff has been heavily involved for many years in the listing of controlled drugs, working with DEA, working with the National Institute on Drug Abuse with respect to pharmaceuticals that are controlled because of the liability for addiction that is associated with those drugs. The scheduling that takes place and the administrative process that goes into determining what schedule should apply to a particular drug is handled in part by Health Assessment Policy staff.

RO: This is both domestic and international?

JW: Yes. Once a year there's a meeting in Vienna, I think, or sometimes in Geneva under the auspices of the World Health Organization involving scheduled drugs, because there can be problems in scheduling in different countries. If it's unscheduled in this country but scheduled in a foreign country, we may not be able to ship it to that country. There are international agreements that can obligate the United States to control a drug even though scientists in the United States feel that there's really no potential for abuse because of some other aspect of the drug. It's just not something you would want to boil down and extract and try to abuse.

RO: Is your experience such that some of the foreign countries are more lenient on scheduling a drug than the United States?

JW: I think it works both ways.

RO: Depending on the country.

JW: Well, depending on the drug and then the arbitrariness of the situation where somebody decided that it needed to be regulated, or the quality of the evidence that was used to defend the position or to corroborate the position that it ought to be regulated. The evidence might not be that imposing, or the situation can be different in that country than in this country.

RO: What about third world countries?

JW: I really don't know anything about . . .

RO: I was just wondering . . . I thought I had read where things were much more lenient in some of those countries than in the United States.

JW: Well, in general they certainly are, you know with labeling requirements, with any requirements. One of the problems that has plagued FDA over the years has been the awareness that pharmaceutical firms in this country are shipping products to less sophisticated countries than the United States and not using full disclosure on the label, not telling them as much about the adverse effects, and just sort of ignoring that obligation by saying, "Well, it meets the requirements of the country into which it was imported," which is deceitful.

Another thing that the Medicine staff has been involved in has been alternative therapies. Congress, you know, decided that they were going to be magnanimous and use taxpayer money to support investigations of therapies that are alternatives to traditional approaches. So Health Affairs has been working with NIH on that and trying to keep some semblance of reasonableness in the whole process so that it doesn't become a grab-bag for quacks who try to dip into that and simply get federal money to carry on activities that are not in any way beneficial to patients.

One of the problems in that area . . . There's a Dr. Freddie Hoffman on the Medicine staff who has been working with NIH on this. One of the big problems is

that when you go to investigate alternative therapies, whether they're herbs or whatever they are--you know, the problem that existed with whole leaf digitalis for a century or more--it's tough to standardize from batch to batch. And you want to study it and you want to correlate what happens when you administer a specific dose to a person who weighs so much or is a certain age and is male or female; you know, it's just so haphazard you can't come away with any conclusion if you're not too careful. What Health Affairs is involved in is trying to explain FDA's requirements for enough rigorousness to make the outcome meaningful and to enable people to learn something from the research, to arrive at a conclusion that's defensible and can be applied to different patient populations.

Now the thing that I've been heavily involved in goes back to an interesting occurrence in 1983. I was acting supervisor in that Office of Health Assessment Policy staff, and Dr. Harry Merriman who was an official with the American Red Cross and still is, he and a woman named Mary Douglas came to my office and talked to me about the possibility of FDA supporting the American Association of Tissue Banks in their effort to develop voluntary standards. And I said, "Oh, I'll be glad to present your request to agency officials." So I talked to Dr. John Petricanni who had worked with the American Association of Tissue Banks in the past and knew something about tissue banking and tissue transplantation.

So we set up this meeting with Paul Hile and other agency officials to discuss the possibility of providing financial support to the American Association of Tissue Banks to develop standards that would help prevent the transmission of communicable diseases in transplants and also standards that would help to preserve the integrity of the tissue after it was processed in some way, terminally sterilized or whatever. And so we had the meeting, and Paul felt that the agency should not provide financial support. At that time Paul had combined . . . You know, the coup had taken place, and Paul was in effect both EDRO and the associate commissioner for compliance. Paul felt that such contributions should not take place. So we told them that.

But Frank Young, who I think was commissioner at the time, said that we should maintain our liaison with them nonetheless, and the American Association of Tissue Banks had wanted me to sit on their board of directors. And we decided, and Paul particularly, that that was not a good idea; and Frank Young said it was not a good idea--and that was correct; it wasn't a good idea--but to keep in close contact with them and encourage them in development of guidelines and standards that would upgrade the quality of the tissue that was being transplanted.

RO: Do you recall, Jim, why Paul Hile was opposed to the proposal?

JW: Oh, yes. That's a very important point. Paul's argument was that if we were to give them financial support, we would soon have a line outside the door of people looking for money to help them in their efforts to develop guidelines, or educational materials, or standards, or you know, for all sorts of things, and we'd simply be overwhelmed with such requests. But I think he had a darn good point. So we didn't do that, but I did maintain close liaison with them, and I worked with them over the years, attended their annual meetings, arranged workshops where FDA would bring in FDA people to speak on particular subjects having to deal with tests that were available, like the Elisa test for HIV or tests licensed by FDA for the detection of hepatitis B, surface antigen, or things like that.

At one of their annual meetings a few years ago in Baltimore, we put on a colloquium that involved about six or seven FDA speakers and a bunch of speakers that were provided by the American Association of Tissue Banks. What happened there was we got a representative of general counsel, Ann Wion, who is extremely knowledgeable about the application of the Public Health Service Act and the FD&C Act to things like this. She's been an advisor to the Center for Biologics for a number of years.

And the American Association of Tissue Banks has a reproductive council within their group that consists of sperm bankers and those operating in vitro

fertilization clinics and things like that. So they were interested in perhaps being regulated by FDA, and so were the tissue bankers. So FDA over the years had gotten involved--almost accidentally--but had gotten involved in individual tissues here and there. We have regulated human umbilical cord grafts for many years. I think they were regulated to some extent by the old Bureau of Drugs. That may have been one of the transitional devices. But currently they're regulated by the Center for Devices. I think they treat the grafts with glutaraldehyde, much the way they do with pig valves, you know, porcine heart valves.

There's a company that came to the Center for Devices and said they were taking corneal lenticules, which are little slivers of the cornea and freezing them, putting them in a cryolathe and machining them so that they have specific optical characteristics and then giving them to the surgeon to stitch to the native cornea, and they would serve as a living contact lens after the native lens had been removed. They were substituting for intraocular lenses, for spectacles, or for contact lenses. So the center felt they needed to be regulated, and they regulated them as investigational devices. And it's still bouncing around over there. I don't think there's a PMA that has been approved yet.

There's another tissue that is a covering for the brain that is very tenacious and can be used as a blowout patch in other patients after brain surgery, so that's recovered from cadavers. That's called dura mater. There's an uncommon disease, Creutzfeld-Jacob disease, that's ordinarily kind of a one-in-a-million thing, but it's been transmitted through the use of dura mater in several instances where the dura was supplied by a firm in Germany. This has occurred in Spain; it's occurred in Australia; and it's occurred a few times in the United States. So the Center for Devices regulates dura mater. They have an import alert for dura mater from the company in Germany that provided the suspect material before. And they regulate sort of as a class II device dura mater that's recovered from cadavers in the United States and processed and distributed from tissue banks to neurosurgeons or other

surgeons, because there are other things you can do with dura mater. It can be used as reinforcement in other parts of the body.

So there are a few things like that. Propagated human skin cells are regulated by the Center for Devices. And then they got into human heart valves. The center was regulating prosthetic valves and has been for a long time, and they regulate them from design to implantation. They were regulating pig valves, the porcine heart valves, that have a little ring stitched on that they call stenting, and then are sewed in. And both of those have problems. The prosthetic valves require the use of anticoagulants, and in women of childbearing years or in children that can been pretty hazardous; the pig valves tend to calcify after a number of years; and human heart valves have some very definite advantages. So they have come into use.

They are recovered from hearts that might not be suitable for transplantation, and they're frozen under a careful protocol, and then they can be shipped around the country, and thawed a few degrees at a time, and implanted. And there's some long-term data from Australia on the use of these. A doctor named Mark O'Brien has what's probably approaching twenty-year data for these human heart valves. But anyway, the Center for Devices decided that they had to regulate those, and so they've undertaken that.

Well, this nibbling at the edges approach sort of alarms people, you know, practitioners--surgeons, tissue bankers--and they would like to see some more systematic approach to it. So in recent years we've been preparing them for the regulation by FDA of tissue banks and sperm banks. And I've been working with CBER, with the American Association of Tissue Banks, and the transplant community, and more recently with Mike Taylor's office of the deputy commissioner for policy on the development of an FDA program to regulate these.

Senator Simon's office has become interested in this, partly because the University of Chicago is big in heart valves, and the Burditt law firm has sued FDA on behalf of some of the heart valve processors because of the way we went about

regulating heart valves and not giving them more time to come up with a PMA and so forth.

(Interruption)

JW: The law firm in Chicago sued because their clients felt that the manufacturers of porcine heart valves, for example, had been given much more advance notice on what was going to be required of them and time to gather the necessary information.

RO: Now when you're talking about this suit, that involves human heart valves.

JW: Yes, that involves human heart valves. So anyway, by whatever means, Senator Simon's office became interested in this, and one of the law firms in D.C. was engaged by processors of heart valves to come up with prospective legislation that would allow FDA to regulate tissue banking and maybe force FDA to take a little different approach with respect to heart valves. Well Congressman Wynden, Ron Wynden from Oregon, has also become interested in tissue banking and the regulation of tissue banking.

Albert Gore, when he was still a Senator, was interested in the regulation of sperm banks. And in fact he and some other representatives in Congress got the Office of Technology Assessment to do a study on artificial insemination in the United States. They came up with a report, and then then-Senator Gore held a press conference and released a talk paper on the report and complimented FDA for the way it regulates the blood industry, you know, and blood banking and so on, and complimented FDA on its ability to assure the safety of the blood supply, and criticized FDA rather severely for not doing the same thing with respect to sperm banks.

So there is interest on Capitol Hill to get this done. We have worked with representatives of Wynden's office and met about three times with a legislative

assistant to Senator Simon and worked with them, and we're still going along in that vein now. As a matter of fact--I don't know if it belongs in a report like this, but--I hope to work for the Center for Biologics to assist them in the development of FDA policy with respect to the regulation of tissue banks and sperm banks and the implementation of any regulations that follow the passage of legislation.

RO: You said Biologics, but you also said that Devices right now has . . .

JW: Yes. That's right. And it sounds incongruous, but Biologics will probably have primary responsibility for the regulation of tissue banks and definitely for sperm banks. They will coordinate their activities with the Device people and may indeed use Device authorities--if that's the way it goes--to regulate some of the tissue.

RO: When you say tissues, you're talking about organs?

JW: No, no. We're not talking about solid organs or what are sometimes called vascular organs, like heart, lung, liver, kidneys, and pancreas. Those are not extensively regulated at all. The Health Resources Services Administration (HRSA) does have responsibility under the National Organ Transplant Act of 1984 to provide grants to promote recruitment of organ donors and also to provide a grant to the United Network for Organ Sharing, which is a private organization, to set up an Organ Procurement and Transplantation Network (OPTN), which is a computerized system, to try and match prospective donors with prospective recipients of organs. Membership requirements in the OPTN call for mandatory testing of donors for HIV and hepatitis. So there is some regulation there, but it's scant.

RO: Well, it's voluntary, or is it?

JW: Well, the organization is voluntary, but to belong and to get an organ you have to play by those rules. And what HCFA does, Health Care Finance Administration gets into the act and says, "We administer Medicare and Medicaid, and if you don't play by these rules, you can't be reimbursed--not only for the transplant; we won't allow you to be reimbursed for anything that you'd be eligible for under Medicare."

RO: I see.

JW: So potentially it's a big economic stick that HCFA holds over transplant hospitals in defense of HRSA's operation. So HCFA is really helping HRSA to enforce what it is encouraging the United Network for Organ Sharing to do with its organ procurement and transplantation network. So it gets tortuous, you know. It's just so complicated. But what a lot of people in Congress would like to see and what the community itself, what the tissue banks want, what the sperm bankers want, is enforceable national standards that will require a certain rudimentary level of safety as applied to everything that is obtained and transplanted.

In other words, uniform donor screening and testing and record keeping, and they want FDA to impose those obligations one way or anther. And they're supporting those in Congress who are studying this issue and encouraging them to involve, to pass legislation that will require FDA to step in and aid in the development of a national standard. We don't have to set the standard: we can adopt somebody's standard; we can get advisory committees to tell us what the standard ought to be. That part is open, but they want FDA to be responsible for seeing that this gets done.

What we have been contemplating is a registration program that would give us an establishment inventory that's accurate so we would know, for example, how many eye banks there are. We're pretty close. We know there are more or less a hundred, because the Eye Bank Association of America has that list for us. And we

get some information from the American Fertility Society and the American Association of Tissue Banks on the number of sperm banks and multiple tissue banks. But there is always some physician in his own office who has a donor that he trusts, maybe another doctor that he's associated with, that he uses as a sperm donor and never tests, you know. All sorts of things are possible. The state of New York is the most advanced in the regulation of sperm banks and tissue banks. When they inaugurated their program they found that there were about four or five small physician-sponsored sperm banks that were operating in a way that they felt was not safe, and they forced them to stop.

RO: Do some of the states have requirements?

JW: Some of the states have requirements: Michigan, Indiana, Illinois, New York, Florida--this is with respect to sperm banks. Montana has an AIDS Prevention Act. There are quite a few states that will say that for artificial insemination from someone other than the husband or the regular partner of the recipient, you know, you have to first test for HIV. And several of them have followed a recommendation that we joined with CDC in offering to the public in February of 1988, and that is that donor's semen be quarantined for six months at least.

You test the donor when you take the specimen, then test six months later for HIV or hepatitis C, and you have allowed six months for antibodies to develop so that they're detectable; because you could take semen from someone who was infected a week earlier and you'd never know it. You could test them, and it wouldn't show up. The HIV antibodies wouldn't have built up to a level where they were detectable, and that might take a month, six weeks, but allowing six months will give you pretty good assurance based on what FDA's Center for Biologics knows about tests for HIV and what CDC people know from epidemiologic evidence that if you wait six months about 95 percent of those infected will have seroconverted.

And you also screen your sperm donors. You get a social history on them, a medical history, a physical, and all that kind of stuff.

RO: Well, how are these semen samples going to be . . . Under what conditions are they going to be stored for six months?

JW: Frozen.

RO: Will these antibodies develop in a frozen state?

JW: No, it's the donor you retest. You bring the donor back, and if he's not available you throw it out.

RO: OK. I see.

JW: And that's for any living tissue, too. They've also said that if you're going to take . . . It sometimes happens in hip prosthesis surgery where they'll put a metal cup on the head of the femur, and they'll take the bone head and remove it in order to do this operation. Rather than throw the bone out. it's sometimes used, you know, ground up, or powdered, or pieces of it taken and used elsewhere in some other individual. So the policy of the American Association of Tissue Banks now is that if you're going to take any living tissue, you quarantine it in a freezer--quarantine it for six months--and get that donor back and retest that donor at the end of six months.

RO: The fact that a number of states have requirements or regulation, is the federal government getting concerned that you're going to maybe fifty different requirements out there?

JW: Well, the practitioners are getting concerned.

RO: I would think so.

JW: Part of the impetus to getting FDA involved is the realization that if the states pass different requirements--maybe New York's is much stricter than somebody else's--it's going to interfere with interstate commerce. And there is a fair amount of interstate commerce in something like this in certain parts of the country. In some parts of the country you'd recover the tissue and distribute it within a few hundred miles, and it would probably stay within the state; because when you go outside the state they've got their own sources.

But on the other hand, with something like sperm banking, you don't have that many sperm banks of the large type, and, you know, they screen their donors well, and they look for genetic diseases. They'll take a three-generation history from a donor, and if there's evidence of premature death from heart disease or cancer in the family, even though the donor is as healthy as a horse, they won't accept him. So that lends a certain attractiveness to samples obtained from somebody that's willing to take such a rigorous approach to donor screening and testing. So they may ship their samples across state lines any time.

RO: What's your feeling, Jim? It seems like we're probably further along having federal requirements for semen banks than we are for tissue banks. What's your feeling about when that might happen?

JW: Well, now, that will be determined by the speed with which something happens in Congress. Senator Simon was very much interested several months ago, and he wanted to get a bill introduced. Then it languished a little bit, because the things that were being offered to him through the law firm in D.C. weren't really acceptable to FDA, and even though FDA doesn't have an official position, those of

us who have been working in this area kind of took it upon ourselves to say, "This will never fly." It was too antagonistic to FDA's traditional compliance mechanisms, the sanctions we could take. There was nothing in there that said a product could be seized. Then the FDA people would say, "Wait a minute. That's too different from what we do everywhere else." And if it wrote in penalties that were trivial by comparison with our other sanctions, that would be pointed out.

But (there were) a lot of other things, too: that we weren't going to turn over our authority to any voluntary group and say, "You do it on our behalf. You set standards, and you do inspections for us and give us the results, and we'll issue permits to the people who pass." You know, it's got to be more careful than that, and we have to be more involved than that, and then we have to . . . You know, the best way would be to have FDA do the inspections and make the judgments. But FDA's got to make the judgments no matter who does the inspections. And while we may have to defer to political reality here and there, things like user fees and, you know . . .

RO: Which are popular now.

JW: Yes, which are . . . You know, user fees cause politicians to salivate and accountants to go into hysterics, but they are politically acceptable. So things like that are being worked out. If Congressman Wynden seems interested in pursuing something rather promptly, gets something worked out with Congressman Dingle that Dingle will accept and maybe negotiate with Senator Simon, and they come together and say, "Sure, this can be introduced at roughly the same time and with few modifications or differences in both houses of Congress; let's go with it" . . .

RO: The trouble with Congress, you know, trying to establish these things that really should be left to the scientific community.

JW: Well, they wouldn't spell out the details. It would be something like empowering FDA to publish regulations that would impose something comparable to good manufacturing practices on the way in which recovered tissue is processed, something that would minimize the likelihood of transmission of infectious disease, minimize the likelihood of undermining the integrity of the tissue, you know, that kind of stuff.

The law itself might be fairly specific in saying that tissue will be defined in a certain way, and that this human tissue intended for transplantation will be covered by this amendment to the Food, Drug and Cosmetic Act or whatever, and somatic cell therapy will be outside that because that's going to be a licensed biological, or bone marrow transplants will be outside. Maybe solid organs will be outside except that anybody who recovers organs for shipment to another facility or to take back to their own facility will have to assure that the basic information about the donor's communicable disease status is determined before that. And the legislation may never go that far. It may be that whole organs are excluded from this entirely.

RO: It will be interesting.

JW: And there will be lots of things that FDA does, especially the idea of cell cultures and somatic cell therapy, combating genetic diseases and all sorts of things like that, vectoring a virus or something into a cell, like a cancer cell, and then going after it with an antiviral drug and hoping for the best, and that kind of stuff would not fall in this area. When it comes time to take cells from the pancreas whether they're fetal preislet cells that have been propagated in culture or whether they were mature cells taken from a cadaver and aggregated some way and encapsulated, maybe, which is one of the things people are trying to do, encapsulate them in collagen so that insulin can get out but white bloods cells that might set up a reaction and cause a rejection can't get in . . . And they're also working on other variations, but that's an approach. And that's the kind of thing that would be regulated as a

licensed biological requiring an IND, and an NDA, and the biological license ultimately.

RO: Another thing, have you noticed any difference in the role that the Office of Health Affairs plays with the commissioners as they change?

JW: Each commissioner has his own style of management. From what I was able to observe, Dr. Hayes used the Office of Health Affairs; he got them involved in human subject protection and things like that. There is not the opportunity to observe every commissioner handling the same type of issues with respect to Health Affairs, because the issues change. When Frank Young came along, FDA was suddenly embroiled in the idea of treatment INDs. And Dr. Young felt that treatment INDs afforded a proposition that FDA could live with, but parallel track was just a disaster waiting to happen. He got Health Affairs involved in helping to put on meetings, to bring in physicians and others to discuss treatment INDs.

His management style was so different that Jim Benson, when he was serving as deputy, talked Dr. Young into going through a fairly elaborate agency process where every center or office came in and they were given virtually an entire day to explain what they did, what mechanisms they had in place, what the function of the office was, and all this kind of stuff. Benson's intention--and I imagine it was an expressed intention, not just an implied intention--was to demonstrate to Dr. Young how many mechanisms were already in place and you didn't have to manage by improvisation, that there were people who did this for a living and were waiting to be plugged in. But I don't think it changed Dr. Young's style a nickel's worth. I think he still felt that he could pick up the phone and call somebody and approach it that way.

But he did involve Health Affairs. He did let Health Affairs get in heavily into this tissue area and into human subject protection and then some of those things. There's another thing that the Office of Health Affairs is involved in called

Tripartite, which are meetings held jointly with representatives of public health officials from Great Britain and Canada. And they meet with the United States every year at a different venue each time and discuss these issues. Health Affairs, of course, coordinates that whole operation and involves people from the various centers and people at the commissioner level talking to counterparts from Great Britain and Canada about regulatory issues and public health issues. I lost the train of thought that I was pursuing there, but . . .

RO: What about Dr. Kessler?

JW: Oh, as far as the commissioner's style was concerned. Young used Health Affairs generously in providing the background material for all those Tripartite meetings. As far as Dr. Kessler is concerned, you know he still uses Health Affairs to a large extent, but I don't think he has nearly so much direct contact with his associate commissioners. He's created kind of a five-headed monster . . .

RO: Yes, or six-headed.

JW: . . . that runs the agency. And additional deputies have been created. I believe Mary Pendergast is a deputy commissioner now, and in addition to deputies for Policy and Public Affairs, you know, and operations and things like this. So the effect on Health Affairs has been to in some ways to scramble the traditional routines of operation, but the functions continue. And Health Affairs, working through the deputy commissioner for Public Affairs, seems to be able to carry out its functions. I guess there's just less direct contact with the commissioner, and there's the added obligation of having to be responsive to multiple deputy commissioners. I mean, in performing a function, you have to be able to anticipate the interest that a deputy commissioner might have, other than the one you report to. Health Affairs reports to the deputy commissioner for Public Affairs, Carol Scheman, as does Alex

Grant, and as does the Office of Legislative Affairs, and the Press Office. They all go through there. But it seems amicable as far as I can tell, and you know, they're able to get their work done. But it does impose the obligation to be able to anticipate the extent to which other deputy commissioners might be involved and make sure that they're invited to meetings or are given the chance to send representatives to meetings on topics that might be of interest to them or where they have some collateral obligation that they have to discharge.

RO: The Office of Health Affairs, then, really has a major responsibility to make sure that the things that they're dealing with that impact on the Center for Drugs or for Biologics or Devices are involved in the discussion.

JW: Yes, and the silicone breast implants is a good example. When that hit with all its force and there were horrendous difficulties in getting advisory committees that were regarded as impartial and all this kind of stuff, because you know, if they involve plastic surgeons or something people felt they had a vested interest in . . .

RO: Sure.

JW: Health Affairs had to jump into that, and we have a physician named Grant Bagley, who's also an attorney, but he would field the complaints coming in from outside through an 800 phone number and try and explain the agency's position and listen to their complaints.

(Interruption)

JW: But this physician, Dr. Grant Bagley, would work with the Center for Devices and the medical community and try and help FDA and all parties concerned keep the situation with respect to breast implants in proper perspective and help people

understand that FDA's concern was with the safety of the recipient, the patient. FDA wasn't trying to make unavailable a worthwhile medical technology; at the same time, it wanted the recipients of such a technology to understand what risks were associated with it.

One of the things that resulted from that was a realization that FDA's relationship with advisory committees probably needed to be looked at. When the Edwards committee was looking at FDA and the total picture, one of the recommendations that they made was that FDA undertake some kind of a study of its relationship with advisory committees and its use of advisory committees. I think there were three suggestions: that FDA use advisory committees as it does now in the consideration of premarket approval application, and also that it use or at least consider using advisory committees to help it manage the agency or make recommendations along those lines, and use them for some sort of general scientific support.

So Dr. Kessler, then, took that idea and thought that it--you know, I'm sure he felt--that it would be unwise to ignore it, because Congress might have an interest, and also the agency could use the continued support of Dr. Edwards and others that were on that committee. So what he did was get a sole-source contract with the Institute of Medicine, and that was handled through the Office of Health Affairs and the Health Assessment Policy staff, and I was the project officer on that contract.

It just so happened that the Institute of Medicine provided a man by the name of Dr. Reddick, who was an extraordinary manager, very, very persistent and demanding of the people that he worked with. And we worked on the requirements for the contract and tried to make them as specific as we could so we would get something for our money. And the contract itself was over $500,000 and ran for a year. But what they did was they got Dr. Larry Early, who was a professor at the University of Pennsylvania, and who's an extraordinary person himself, both from the standpoint of discernment and managerial ability.

And they went out and they recruited a group to look at the way FDA uses advisory committees. They got Dr. Crout, who had been Director of the Bureau of

Drugs; they got Hank Meyer, who had directed both Biologics and Drugs; they got Dr. Windom, who had headed NIH; Dr. Carolyn Davis, who had headed HCFA. They went to industry and talked to them. They talked to advisory committee members current and past, talked to all sorts of people in FDA, and then came out with a report and some recommendations that were really worthwhile.

There were some humorous aspects to it. When they were considering the idea of whether or not FDA should utilize advisory committees to advise it in the way it manages the agency, Dr. Windom and Dr. Carolyn Davis were adamant that FDA should never even consider such a thing. Windom said they did that one time at NIH, and he said your biggest problem is how to dispose of the recommendation without doing anything with it. (Laughter) That it's utter folly to invite ignorant individuals to tell you how to run your business, because they have no conception of how it really works, and they come up with all sorts of inappropriate advice you then have to contend with. So they made it very clear that they thought that was one of the dumbest ideas (Laughter) that could be considered. And of course, it didn't get any place.

And their recommendations were for the way in which FDA currently uses its advisory committees and how to handle conflict of interest and things like that. They had Dick Merrill, who was a former general counsel at FDA, on that group, and he paid particular attention to the question of conflict of interest: how to make sure that the advisors don't have conflicts of interest, but at the same time that you don't wipe out everybody who's bright enough to have an opinion. The fact that they've stood up in public and said something doesn't mean that they can't impartially evaluate data that you've given in support of a specific application. So there's got to be a reasonableness to the whole thing.

But that concept worked out pretty well, and Health Affairs had a big part of going along with that and getting the Institute of Medicine in contact with the appropriate individuals in FDA who could . . . The committee management people in the centers especially, who were very, very knowledgeable and had years of

experience in setting up advisory committees. And they came across all sorts of things that someone, you know, like me, who had never been involved in this, would not have anticipated: such things as how you seat the advisory committee. Do you put the secretary and the other FDA people together and then have all the advisors across from them or something? Or do you use a round table? That consideration wasn't frivolous. I mean, they were dead serious in what they were considering and in evaluating the recommendations that came to them, including from people in FDA.

Then it was interesting that different division directors in the Center for Drugs used advisory committees differently. Some were more imperious than others, you know, and they want somebody to validate what they had already decided. And others really wanted some input from people who had clinical experience that couldn't be duplicated within the agency. So you have all the dynamics of human personality and training and experiences that get involved in it.

RO: Well, Jim, is there anything else? We've covered a lot of things here, and it's been . . .

JW: I don't think we have overlooked anything of merit.

The Office of Health Affairs was also involved as an impartial third party in consideration of DESI denials. As you know, the National Academy of Science, National Research Council made its recommendations and the Bureau of Drugs handled its part of the thing and tried to take products off the market. Then companies would protest and hearings would be held, and the administrative law judge would read over the results of all this, the transcripts of the hearings and so on, and make his judgment. Usually it would be in support of the bureau. The pharmaceutical firms would protest this, using the legal process that was open to them, and so Health Affairs then would undertake a review of all that had happened.

And we'd get a member of the Office of General Counsel to work with us in deciding the issue.

For example, I worked with Mary Pendergast on oral proteolytic enzymes. Mary literally had about seventy-two boxes of study data in her office, and she went through that meticulously. It was one of the most thorough jobs I have ever seen. You know, she didn't have the background in science, but she relied on Health Affairs to provide some information there and for us to get together statisticians and physicians. We used a doctor who at that time was on our staff, Dr. Tom Holohan, and were able to resolve it.

But there were several issues like that, and Health Assessment Policy staff is still working on DESI trying to finish up the last few drugs that are in contest in one way or another. At times we've gotten involved in FDA's recall operations. Dr. Nightingale worked on a health hazard evaluation form that was recommended to the centers for use and that Paul Hile then incorporated in the recall manual that was part of regulatory procedures.

There was a time in the early to middle eighties when we would get copies of Class I and II recalls and the background information, and we would get involved in making some sort of a judgment as to whether or not the classification assigned to the recall was appropriate and whether or not the level of effectiveness checks was consistent with the classification of the recall. If you're going to make it a Class I recall and have no real effectiveness checks, what purpose did the Class I designation serve. And you know, or the other way around. If you had so many effectiveness checks that it was inconsistent with a Class II recall, maybe you better take a second look if the hazard was more severe than at first thought.

But we got quite involved in that, and then there's just generally speaking a lot of commissioner correspondence that comes to Health Affairs at Health Assessment Policy staff, things that are written to him questioning certain things--Why was this taken off the market? And we might have to coordinate with other units in FDA including the centers, but we would respond. Or if something was

removed and a doctor felt that it should not have been--this sort of stuff. We'd respond to that.

And we got involved in the issue of quackery. People were coming to FDA complaining about physicians promoting the use of chelating agents for the treatment of atherosclerosis and other diseases. It was a manufactured indication. They wanted something done about it, and Health Affairs would try to serve as a go-between or try to investigate it and try to put forward something that could be adopted by the agency as a policy, and never really succeeded in getting FDA to take a firm stand against quackery of this type.

The agency through its field force would investigate individual instances of something based on complaints, especially if someone were promoting or manufacturing, you know, the claims that they can make--labeling. That was relatively easy. Where it became more difficult was where drugs were properly labeled, but physicians would take something like EDTA and misuse it in their own practices. And they would make claims, write a book, or anything. You could seize the book, but once it was out there and people bought it and read it and it extolled the virtues of EDTA in treating heart disease or cardiovascular disease in general, there was a market created. They would get patients and they would treat them that way.

State licensing bodies for physicians would have hassles with legislatures in their own states. Legislatures would want to legalize unsupported indications that were not part of the labeling approved by FDA, and FDA would have to respond to that in some fashion, and the state medical licensure groups would get involved and try and defend traditional methods. So Health Affairs got involved in that. And I guess that's about all the major things.

RO: Well, Jim, we appreciate your giving your time on this.

JW: Oh, I'm happy to do it.

RO: And unless there's anything else, we'll end this interview.

JW: No, that's fine. Thanks very much for the opportunity.