

**History**  
of the  
**U.S. Food and Drug Administration**

**Interviewee:** Marlene Haffner, MD, MPH

**Interviewer:** Suzanne W. Junod, Ph.D.  
Robert A. Tucker

**Date:** December 6, 2011  
March 13, 2012

**Place:** Rockville, MD

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Public Health Service

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

DATE: December 6, 2011 & March 13, 2012 PLACE: FDA, Silver Spring, MD LENGTH:

INTERVIEWEE:

INTERVIEWER(S):

NAME: Marlene Haffner, MD, MPH

NAME: Suzanne W. Junod, PhD  
Robert A. Tucker

ADDRESS:

ADDRESS: Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20903

FDA SERVICE DATES:

FROM: 1981

TO: 2007

TITLE: Director, Office of Orphan  
Products Development

INDEX

<u>Tape</u>	<u>Page</u>	<u>Subject</u>
1 - A	1	Personal & educational background
	10	FDA employment
	11	Bureau of Medical Devices
	14	Shiley Heart Valve
	16	Yorick the skeleton
	17	Dalkon Shield
	19	Center for Devices and Radiological Health (CDRH)
	21	Deputy Director, Office of Orphan Products Development
	21	Director, Office of Orphan Products Development
	22	Kefauver-Harris Amendments (1962)
	23-25/31	Orphan Drug Act
	25	Huntington's Disease (Chorea)
	26	Orphan Drug Act Amendments
	28	Adenosine Deaminase/Bubble Boy
	31/42	Orphan Drugs and Europe
	31	Orphan Drugs and Japan
2-A	32/42	Orphan Drugs and Australia
	34/37	Orphan Drug Act
	35	AIDS/AZT
	37	Therapeutic Foods
5-A	41	Orphan Products and Standards

<u>Tape</u>	<u>Page</u>	<u>Subject</u>
	42	Chemical Medicinal Controls (CMC)
	43	Senator Howard Metzenbaum (Ohio)
	46	Gamma-hydroxybutyrate (GHB)
	46	Orphan Drug Act
	57	Thalidomide – Approved as an Orphan Drug
5-B	52	Cutting Edge work with Orphan products
	54	“Lorenzo’s Oil” – the movie
	56	Grants Program
	61/62	Orphan Drug Act

Interview with Marlene E. Haffner

December 6, 2011

TAPE 1, SIDE A

RT: This is another in the series of FDA oral history interviews. Today, December 6, 2011, the interview is with Dr. Marlene E. Haffner. The interview is taking place on the White Oak campus of FDA in Silver Spring, Maryland, and interviewing Dr. Haffner is Dr. Suzanne Junod and Robert Tucker of the History Office.

So, Dr. Haffner, please provide a brief overview of your personal and educational history; for example, where you were born and raised and educated, then moving into your career in the FDA and the Public Health Service.

MEH: I'm Marlene Haffner. I was born in Cumberland, Maryland. Both of my parents were physicians, and all I ever knew was that I was going to go to medical school, I guess in part because I didn't know anything else, and in part because it was something I really wanted to do. My parents made house calls, or my mother did, and I grew up in people's living rooms waiting for her. And so I set out to go to medical school, left college after three years, never got an undergraduate degree, and matriculated at

George Washington University School of Medicine here in Washington, D.C., and it's there that I met my husband, Bill, who was also a medical student. We were back-to-back over cadavers. He had a female, I had a male, and so we exchanged information as the anatomy course continued. And then we began dating, and between our second and third years of medical school, we were married; and made a commitment to each other that (a) we would never compete with each other, and (b) that we would do different specialties, because we thought that that would help as far as being noncompetitive.

He then became an obstetrician-gynecologist, I became an internist with a subspecialty in hematology and also a fellowship in dermatology. My husband got a draft deferment for the Vietnam War, which was ongoing at that time, and that deferment gave him the option of either joining the Army or the Public Health Service. He chose to join the Public Health Service and received orders to the Navajo Area Indian Health Program, and, needless to say, I came along.

We had two small children at that time. Our older daughter was two years old and our younger daughter was four months old.

We moved to Gallup, NM and Bill was a teacher in one of their health ancillary provider programs, and I was chief of the Department of Internal Medicine at the Gallup Indian Medical Center, a tertiary healthcare facility serving the Navajo Reservation. I served for a little over three years in that position, beginning in 1971.

In 1974, during a conversation with the physician who directed the entire Navajo Indian Health Program, he asked me to apply as Director of the program because he was leaving. I did apply, I was appointed, and at the age of 33, with, quite frankly, no knowledge of what even an organizational chart was, I became Director of the Navajo Area Indian Health Service, an area covering roughly the size of the state of West Virginia, 25,000 square miles. I had 2,000 employees, a budget of \$33 million, and I had the best time working with the Navajo people and further developing their public health program. And the Indian Health Service is one of the few if not the only, true public health programs in the United States. It provides acute care, chronic care, preventive care, dental care, water and sanitation, and some long-term care. So we're talking about a truly comprehensive program, and I was in the middle of it with the best staff, and they helped me learn how to manage, and it was a very good fit.

We stayed with the Navajo Indian Health Program for 10 years. I was the Director of the program for seven years.

RT: Now, you mentioned your husband went into the Public Health Service. You later did?

MEH: Yes. He went out as a uniformed member of the Public Health Service. I came out as a civilian and four years later converted to Commissioned Corps. It was a program in which I was always interested, in which I had believed very, very strongly. When we first moved to the Navajo area, quite frankly, I couldn't afford to also join the Commissioned Corps because the salary disparity was just too great between Commissioned Corps and civilian. I think my entrance salary was \$14,000, which was a fair amount of money in those days. It may have been more than that. It may have been that Bill's was \$14,000 and mine was \$21,000, but by comparison, Corps salary was much less.

We never thought we would stay beyond two years, but we found that we just loved the program, and my husband and I had always been interested in serving the underserved. We had looked at Project Hope, we had looked at the Peace Corps, we had looked at a number of programs, and for one reason or another we weren't able to do it, so the Indian Health Service really met our needs.

RT: I was wondering, you were administrator. Were you involved in the medical care of patients or . . .

MEH: Yes. I was administrator of the entire health program. I was not administrator for schools. That's the Bureau of Indian Affairs, which is part of the Department of the Interior. My job was healthcare programs. So I ran seven hospitals, 200 plus clinics, and a variety of other health stations during that period of time. Now, clearly, I didn't do all of that myself. That's why there were 2,000 employees.

RT: In your medical degree, did you also include training as a surgeon?

MEH: No, no. I was an internist. Internists do not do surgery. They might remove an ingrown toenail or stitch a wound, but, no surgery. The only surgery I knew was what I had learned in medical school, and I had learned some surgery in medical school, but, I dealt with adult medicine. And we still did see a lot of infectious diseases when I was on the Navajo Reservation, meaning that there was an outbreak of diphtheria and we took care of that. There was still, more tuberculosis there than you would see in the general population.

RT: Well, that was kind of a malady of the Indian population in the earlier periods of their . . .

MEH: It was indeed, and it was on the Navajo Reservation that the initial treatments for TB - Isoniazid (INH), streptomycin, ethambutol -- were developed. That was well before my time, but that did go on the Navajo Reservation, and the Navajos were very proud that they had taken part in that and that TB had become far less prevalent, although we still did see cases and were always making sure that we looked out for it. We saw plague, we saw tularemia, some of the other diseases that most physicians don't ever see unless they go to a developing country.

RT: And the climate probably was conducive to healing or therapy too, wasn't it, in the Southwest?

MEH: Well, we talk about the Southwest as being good for lung diseases and so forth. I think that's been pretty much debunked as not true.

The state of New Mexico is actually a pretty high state. One thinks of the Southwest as warm, but that's Arizona for the most part. In New Mexico the lowest point is 2,300 feet elevation, and the highest point is Wheeler Peak, which is 12,000 plus, maybe 13,000 feet. Where we lived, in Gallup, New Mexico, the elevation was 6,750 feet, meaning that in the wintertime we got snow and ice. Snow usually melted by midday. I measured how bad a winter was

by how often I slid from the road in my car. Never had an injury. But I do remember once, in May, being literally blown off the road. The winds were so strong and it was snowing, and the snow was sticking and it was pretty slippery, and the wind was blowing and my car just blew off the road. And I sat there for a while, and it cleared a bit, and I put it in gear and drove back on the road.

RT: I think that . . .

SJ: No cell phones.

MEH: There were no cell phones. I did total a government car once two miles from Whiskey Creek, which I called "10 miles from Navajo Lake" as I thought that sounded better than Whiskey Creek. I totaled that car because I came over the top of a hill, and it was absolute black ice ahead of me; there was nothing I could do about it. I kept my foot off the brake, but the car still slid off the road and went head-first into a ditch.

RT: Fortunately, you -- were you injured or . . .

MEH: I was not injured. My hardboiled egg that I had for lunch was completely demolished. My seatbelt was on, and I had sandals on, so I had trouble getting out of the car because it was kind of deep snow, but I did get out, and I hitchhiked. It was the Director of the Bureau of Indian Affairs who stopped and picked me up and said to me,

"Oh, Dr. Haffner, I've been meaning to call you," and so we had a wonderful conversation while he took me to my meeting. And when I got there I called the appropriate people, who came and towed the car away, and I got a ride back home. It was a lot of paperwork, though.

RT: I was kind of surprised to learn from a college friend that there was skiing in parts of that state, and I didn't realize it.

MEH: Oh, yes. There's very good skiing. In Taos, New Mexico, we ski every year still today, good skiing. I'm looking forward to it this year.

RT: So, was that pretty much the area of your service in the Health Service, for the Indian Health Service (IHS).

MEH: For direct care services, yes. And I was proud of many of our accomplishments. Our hospitals were JCAHO accredited. We were able to bring the . . .

SJ: The JCAHO? Clarify.

MEH: Joint Commission on Accreditation of Hospitals. Sorry, thank you.

Our neonatal death rate, which is the death rate of infants in the first month of life, became lower than the national average. In other words, we were better than the

rest of the nation, and we attributed that to better prenatal healthcare.

It was an excellent experience. I felt like what was done was good, the program I was directing was a world-class program, and was well recognized as such.

And I, also, felt that from a family standpoint, our children learned a tremendous amount. They went to reasonably good schools, and our family life was excellent.

And then in 1981 we moved to the Washington area. The kids were ages 10 and 12, so the end of grade school, the beginning of junior high school, and they fit right in. It was at that point in time that I joined the Food and Drug Administration in what was then called the Bureau of Medical Devices. I was Director of the Office of Health Affairs.

SJ: All right. Now, let me ask this. Was it primarily because of the children that you moved back here, or did you each have jobs?

MEH: It had nothing to do with the children. We would have been happy had the children . . . I mean, the schools were good. How we would have managed high school, I'm not sure they were as good. But they came from an educated home, so I think they would have survived.

But my dad had died; my mother was chronically ill; my sister was going out to Cumberland every other weekend. She was exhausted. And it was time to stop enjoying our life and playing -- we weren't really playing, but it was time to take on family responsibilities.

SJ: So you came back. And did you have a job, did your husband have a job?

MEH: We both had jobs when we came back. I was Director of the Office of Health Affairs in the Bureau of Medical Devices, and my husband was employed at the Uniform Services University of the Health Sciences, The F. Edward Hébert School of Medicine. He was Director of Educational Training Programs in the Department of Ob-Gyn. He was by then a Captain in the U.S. Public Health Service. I had been promoted to Admiral when I was on the Navajo Reservation. Then when we came east, I reverted to Captain but was promoted later again to Rear Admiral.

I worked in the Bureau of Medical Devices for five or six years.

SJ: You are one of the early employees working in medical devices since the Amendment was only enacted in 1976.

MEH: Yes.

SJ: We would be interested to hear about your experiences during that period in your career.

MEH: Oh, it was fun.

SJ: And how many people you had and what you were doing, and the marriage between Radiological Health and Devices.

MEH: It was an interesting time. I came in '81, the device law had been passed in '76, Victor Zafra, was the Director. Vic had come from Office of Management and Budget (OMB), Bureau of the Budget, and didn't know much about medicine, nor did he know much about healthcare. And I was surprised when I came to the program how few physicians were in the Bureau of Medical Devices. By few, 10 would be a lot, and there may have been fewer than that. The total number of employees in the Bureau of Medical Devices, I really don't know, 200 or 300, maybe fewer than that.

I had two major responsibilities. One was to introduce device regulation to physicians like the American College of Physicians, the American College of Surgery, the American Academy of Anesthesiologists, all the organized medical groups including the American Medical Association. Because the FDA regulation of devices was something fairly new, it was very new to NIH as well. And so I spent a

considerable amount of my time interacting with those groups, making presentations at annual meetings; attending smaller meetings; discussing what makes a Class I, II, III device; why FDA is regulating; what a clinical trial of a medical device is. I did health-hazard evaluations. I was just sort of inserted in all sorts of places because there were such few physicians in the Bureau; it was a Bureau then.

I was also responsible for the laboratory the Bureau of Medical Devices ran. It was a laboratory that did not test medical devices pre-approval but looked at device failures; why things failed, and if there were ways to predict failures, to understand the device functions better. This was at the time that a disease called toxic-shock syndrome came to the forefront. It was caused by a bacterium, and the bacterium primarily grew on tampons. Toxic shock syndrome occurred most frequently in menstruating women. And the device lab studied the disease extensively and determined the causative agent and how it occurred. And toxic shock has basically gone away, I don't think due to any specific intervention.

SJ: You don't think removing Rely tampons from the market helped?

MEH: It may well have, yes. Was it Rely?

SJ: Yes.

MEH: Okay. Then you're right, that did help. And the other tampons did not grow the bacteria, or did not allow the bacteria to grow.

SJ: The theory was that it was the super-absorbency piece of it, but you're saying it might be the composition.

MEH: It might be, I honestly don't remember anymore. So I would go back to your data and see what you have because I'm pulling things out of . . .

SJ: But we were, I guess the point is we were actually testing these things.

MEH: Yes. We were actually testing them.

SJ: And where was the lab? Was this the PHS lab that we took over or -- we declined one of them.

MEH: No. This was a lab that we were running in the Department of Agriculture building at 12<sup>th</sup> and C Streets. That lab remained there for many years, then moving onto Parklawn Drive and, next door to the United States Pharmacopeia (USP) building.

SJ: Yes, I know where you're talking about. Right. Chapman Building?

MEH: Yes, across the street from the Chapman Building, so I guess it's Parklawn Drive or Fishers Lane

and Chapman Avenue. And that lab was populated by the most phenomenal engineers and biological scientists.

SJ: Names.

MEH: Ed Mueller. Ed had started out in medical devices. He was intrigued with medical devices, with how they worked. Ed retired some time ago.

And the other person that was the co-director of the lab was Don Marlowe. Don retired fairly recently from the FDA, and I think still works somewhat part time on an as-needed basis. He does a lot with the national standards organizations, ANSI, American National Standards Institute; ASTM, American Society for Testing and Materials; ISTM, International Society for Testing and Materials; and worked very hard in the standardization of components in devices on an international basis.

The other area that we looked at besides toxic shock syndrome was a situation where a heart valve, called a Shiley valve, that was made by Shiley . . .

SJ: Sixty-degree concavo-convex.

MEH: That's right. Well, a valve stint was fracturing, and when that occurred, it was an immediate medical emergency. Very few people survived that kind of fracture. And our lab looked at why the valve developed metal fatigue and fracture, and looked at the alignment of

the metal, in the valve. They were able to develop some potential predictions for why the valve did or did not fracture. And Shiley, I think, eventually took that valve off the market and redesigned it.

SJ: Well, there was a previous Shiley valve, and they argued that this was essentially an improvement. And we said no. So it was the first actual full device approval that we did under the '76 Amendment.

MEH: Oh, I didn't know that.

SJ: Yes. And then the struts were fracturing. Anyway, I knew FDA had done a fair amount of work to try to pinpoint more of how to predict that with some imaging techniques and some other things.

MEH: Yes. Don Marlowe can tell you more specifics of that. And it was extraordinarily exciting, and I learned, what engineers can do in, specifically in nondestructive testing. You would like to be able to test medical devices in a fashion that they can be evaluated without destroying them to determine what is going on and whether they will or will not fail. If they are a life-supporting device like that heart valve, you cannot afford failure. They have to be fail-proof, or they have to be predictable as to when they need to be replaced.

We also, at that time in the lab, had a skeleton, who we named Yorick, "Alas poor Yorick, I knew him well," from Shakespeare. Yorick was outfitted with medical devices of every size, shape, and variety, so Yorick had an artificial hip; Yorick had a pacemaker; Yorick had implantable intraocular lenses and a hearing aid; he had an artificial heart in addition to a pacemaker; he had some artificial interdigital spaces; he had a rod for scoliosis, as I recall; he had a penile implant; he had a breast implant; he had a chin implant. Did I say hearing aids? He did have hearing aids. He probably had an auditory stimulator device. And that's what I can recall. He had just about every implantable, attachable device. Oh, he had a shunt for hydrocephalus, and a few other odds and ends.

I traveled with Yorick when I went to medical meetings, and once when I was getting on an airplane and checking this case in which Yorick traveled, the agent asked me what was in my case. So I said, "Just a skeleton." She let me on, but I had to explain that I was working for the FDA and what this was. I did not have to open the case. I threatened to take him out and sit him on the seat beside me, but no one wanted me to do that.

Yorick now belongs to the Smithsonian.

SJ: We should have had right of first refusal.

MEH: Yes

SJ: And at best, we should have traded them for some things that we wanted. It should not have been just handed over. It was very insulting to our office.

MEH: How did that happen? Don Marlowe offered it up?

SJ: No. I think the Smithsonian wanted it . . . but we were disappointed not to have been consulted about it.

MEH: Too bad.

Anyway, Devices went like that for quite a while, and then the . . .The Dalkon Shield.

MEH: Ah.

SJ: You were the one that donated our Dalkon Shield that we have archived.

MEH: Yes, yes, I did.

SJ: As I recall, you weren't directly involved in it, but you may have know people who were involved.

MEH: But I knew enough about it.

SJ: And certainly your husband.

MEH: My husband was involved in it. I always felt, well, it doesn't matter what I felt. The Dalkon Shield . .

TAPE 1, SIDE B

RT: We were speaking of the Dalkon Shield.

MEH: Yes. The Dalkon Shield was an intrauterine device, a birth-control device, which looked like a little beetle. It was about half an inch or so long, maybe three-quarters of an inch, and it had little spikes on the sides sort of like legs, except it wasn't legs. And for women that didn't go to their physician for checkups, those devices became embedded in the uterus and created severe problems, including abscesses. The FDA worked tirelessly with the company -- Abbott?

SJ: A. H. Robbins.

MEH: A. H. Robbins, to bring some, well, the device was long off the market, but to bring some recompense to the individuals who'd suffered damage from the device. And, consequently, I received one of about five Dalkon Shields that came to the agency.

SJ: For which we are certainly grateful.

MEH: And donated it to the History Office.

SJ: It is now on display in the new display cabinets in Building 1.

MEH: Good.

SJ: Okay. So, you were head of the lab?

MEH: Yes. The next thing that happened was that the Commissioner decided that Devices and Radiological Health

should be joined into one organization, and it became, first, the National Center for Devices and Radiological Health, and then just the Center for Devices and Radiological Health, or CDRH with John Villforth as the first Director.

Have you all interviewed John?

SJ: Yes. It isn't finalized; he hasn't signed off on it yet, but he will.

MEH: And so then the question came as to what I would become, and I kept my position as Director of Health Affairs in the new Center, and my Deputy was a man by the name of Gordon Johnson, who had been Director of Health Affairs in Radiological Health. He was a radiologist.

SJ: What was your relationship with Stuart Nightingale at this time?

MEH: I interacted with Stuart. I . . .

SJ: Because he was the agency Health Affairs . . .

MEH: He was the agency Health Affairs. We had a very good relationship, but he didn't have a real program that I could discern, and his issues . . .

SJ: He was putting out a lot of fires.

MEH: Yes. He was doing bigger things, and I was doing down-to-earth stuff. But at the time that I then became the CDRH Health Affairs, I lost the lab. The lab

went over to wherever it is, the Office of something, Testing and Materials? No. Device Evaluation? No. The third one.

At any rate, I missed the lab a lot. And, quite frankly, I became a little bit bored in what I was doing. I didn't have any real responsibilities. I had no line of authority over anyone anymore other than a few staff that had come from Radiological Health, and they were all good people, but we didn't have a reason for existence. And I could not cohesively develop a team because there were no specific missions around which to develop a team.

And so I went to speak with Dr. Young, the Commissioner of FDA, Frank Young, and I said, "Frank, I am bored, and I'm afraid that if I'm bored, I'm not going to do a good job because I don't know what to do a good job at, and I am going to be looking for a job and I'm just letting you know. And whether I will stay in FDA or leave FDA or even leave the Public Health Service, quite frankly, I don't know at this time."

And Frank said, "Will you give me six weeks? I don't want to lose you."

And I said, "I'll give you six weeks."

Six weeks to the day he called me and he said, "Could you come over to my office?" and said when I got there,

"How would you like to become the Director of the Office of Orphan Products Development?"

And I said, "I'm not sure what they are." I had heard one lecture on what orphan products were, given by Steve Fredd, who was the Acting Director, but I really didn't know what the office did.

Anyway, the next day found me in the office, not as Director, but as Deputy to Steve Fredd. Steve . . .

So I came as Steve's Deputy. It was a little uncomfortable at first. Steve didn't know I was coming. He didn't know that he wanted or needed a Deputy. He didn't know that I had been promised the job of Director; granted, he was Acting. And so we danced around each other for a while. And then at about six months, Dr. Young gave Dr. Steve Fredd, M.D., the position of Director of the GI Division, where he did very, very well and was very happy, and I moved into the directorship of the Office of Orphan Products.

We were on the 12<sup>th</sup> floor in the A wing in the Parklawn Building at that time. We had, on paper, 7.4 FTEs. I never did find the .4 person. But I set about learning the program, developing it further, and ultimately hiring an increasing number of people. I stayed for 20 years. When

I left in 2007, just a bit over 20 years, we had somewhere between 20 and 25 members, or 25 FTEs on staff.

The program, again, was very nascent when I came. Marion Finkel, M.D., had been the first Director. She had established the framework and had done it very, very well. She left to go to industry. Steve Fredd was Acting for about a year and a half before I came. And so I was the second full-time Director of the office.

I was extraordinarily grateful for the work that my predecessors had done because it was very easy to build upon that, and build I did.

I, again, continued to do public speaking. I loved to speak publicly, and am invited back, so I guess I do a reasonable job, but I did a lot of public speaking about what orphan products were. No one had an idea what an orphan product was.

RT: Just for the record here, how would you define generically?

MEH: Okay. An orphan product is actually defined . . . Well, let me back up a minute.

In 1962 -- so I'm going back quite a ways -- the amendments to the Food, Drug and Cosmetic Act were passed, called the Kefauver-Harris Amendments. And it was that law that began the escalation of price of the development of

drugs in the United States. That law required safety and efficacy of products to be used as human drugs.

Consequently, as the cost of drug development increased, companies were loath to develop drugs that affected small populations of people, and they didn't. Oh, they would occasionally develop something because somebody's Aunt Nellie had it, or as what they called at that time a service drug, but they didn't develop drugs for small populations. So the Orphan Drug Act came into existence to encourage drug development via incentives. It was passed in 1982 and it was signed into law on January 4, 1983, by President Reagan.

There was considerable discussion before the law was signed, and Mr. Reagan was concerned that the tax-credit provisions of the Act were a budget breaker, and he was going to veto the Act.

In 1983, and still today, there existed a group called NORD, the National Organization for Rare Disorders. NORD was headed by a woman by the name of Abbey Myers, and Abbey is the prototypical example that in the United States, one person can indeed make a difference. Abbey worked very hard, she worked tirelessly, to get the Orphan Drug Act passed. And when she heard that Mr. Reagan might consider vetoing it, she sent a message to Mr. Reagan, I suspect via

Congressman Waxman or the Senator from Utah, Hatch, saying, "Go right ahead and veto it. You don't mind if we take out full-page ads in the *Washington Post*, the *New York Times*, and the *Los Angeles Times*, because that's what we're going to do." Whether that changed the President's mind or not I have no idea, but it makes an excellent story.

The Orphan Drug Act then was signed into law. It amends the Food, Drug and Cosmetic Act, and it had at that time some major incentives. It allowed tax credits for the development of a drug for a rare disease. At that time a rare disease was not very well defined but was a disease, the development of a drug for which would not be profitable. It had a grants provision in it; it had the provision for protocol assistance of developing your drug. Those are the ones I can remember. If I remember more . .

SJ: Protocol assistance from FDA?

MEH: From FDA, yes. Protocol assistance was from FDA. And it had designation of a drug as an orphan drug, which is what began the incentives into being and provided the assistance of the Office of Orphan Product Development for general communication.

It became increasingly obvious that no one knew what profitability was. The profitability portion of the Act was administered through the Internal Revenue Service. It

was part of the tax issues. But no one knew what profitability meant. And so, as a surrogate for profitability, in 1984 the first amendment to the Orphan Drug Act was passed. That amendment stated that an orphan disease is a disease affecting fewer than 200,000 people in the United States. So 200,000 was a surrogate for profitability. The amendment made sure, with that number, that some of the diseases people had been very concerned about, such as Tourette's syndrome, which had no therapy, quite frankly, has no approved therapy now, but is a disease that Abbey Myers' child has, Tourette's syndrome was served; Huntington's chorea, a disease that killed Woody Guthrie, and his wife was a very strong proponent of the Act, Huntington's disease was included.

SJ: Huntington's chorea?

MEH: Huntington's chorea, also called Huntington's disease, and several others of that type.

So we now had a real definition.

Then, in 1985, there was another amendment, and, quite frankly, since I wasn't in the office then, I don't remember what it was.

In 1988 there was a third amendment, and that was the last time that any amendments were passed and signed by the President.

The 1988 amendments specified that a drug had to be designated as an orphan drug prior to the 1988 amendments being signed, which was April 18<sup>th</sup>, 1988. It also stipulated that there should be a study of both foods and devices to determine whether there should be something called an orphan food or an orphan device. Those studies were done, but they had no significant results.

So in March 1986, I came to the Orphan Products Office, became Director in October, 1986. And on the day that I became the Director, the one hundredth designation was signed. There are now, almost 30 years after the passage of the Act, almost 3,000 designations that have been granted.

The law has been called by many as one of the most significant pieces of legislation passed by the Congress in the latter portion of the twentieth century, and we began to see drugs for rare diseases being developed with increasing effort and energy. Mainly, it was small companies that were involved; very few of the pharma companies were involved. In fact, big pharma wasn't particularly interested. Some might say they were against the passage of the Act and the implementation of the Act.

RT: Now, these smaller companies, were they susceptible of grants to help in the development?

MEH: The small companies could get grants, but primarily the grants were given to academic researchers who were making an initial foray into drug development, and many times those grants were grants that would be first-in-man kinds of activities.

SJ: Which would eliminate the need to develop expensive animal models?

MEH: No, no. Animal models didn't change.

The drug development process for an orphan drug is no different than the drug development process for a non-orphan drug. Having said that, the FDA has traditionally been more flexible in looking at how to develop a drug for a small population. If you have a population of 500 people in the United States with a disease, it is exceptionally difficult, if not impossible, to do two well-controlled, double-blind clinical trials. The smallest population which included clinical trials for which a drug has been developed is a drug called PEG ADA or Adagen. Kids with adenosine deaminase deficiency have an immune deficiency, and are unable to fight infection. Prior to the advent of PEG ADA, they had to live in a bubble. Most died by the age of six from infection.

With PEG ADA, which affected approximately 14 kids in the U.S. at the time, and the clinical trial had somewhere

between six and 10 youngsters in it. The drug was approved with one active clinical trial, not blinded, and with historical controls. Enough was known about the disease that historical controls could be used.

SJ: Is this the disease that the public knew as the Bubble Boy?

MEH: Yes.

SJ: Because it made the cover of *Time*.

MEH: Right. This is Bubble Boy treatment.

There had been other drugs developed as orphans where there are no patients, such as drugs to counter bioterrorism, but they are developed under the animal rule, and that came much, much later.

SJ: Let me ask a question that probably should wait till the end, but we'll put it in where we can.

Did the orphan drug program contribute to the evolution of FDA's greater understanding of how to evaluate small clinical trials? I just took (and passed) a course on the subject.

MEH: Right, it is smaller populations what brought that course to the forefront, Tim Coté did that, and I give him a lot of credit for it.

So, in the beginning there was the orphan drugs, and the law said 200,000 was the cutoff point. We had as

small, as I said, as six to 10 patients in a clinical trial, and we had diseases which occurred with greater frequency. One that I recall was the development of erythropoietin for chronic kidney disease or end-stage renal disease, which had at that time 192,000 patients. And we knew the number because they are registered under the end-stage renal disease program administered by the Social Security Administration under Title 18, Title 19 of the Social Security Act.

SJ: As I understand it, anyone with end-stage renal disease, is entitled to complete care at government expense if they want it. Is this correct?

MEH: It's an entitlement. Right. It, too, has been a very successful law, I might add.

SJ: So you had drugs being developed at both ends of the spectrum.

MEH: We are now coming up on 1990, and we are beginning to see an increased interest in orphan drugs in other parts of the world. A man by the name of Dr. Larry Weaver, one of the leaders at PhRMA, the Pharmaceutical Manufacturers and Research Association, Larry had retired from PhRMA, maintained a keen interest in orphan drugs, and he also loved to travel internationally. He met with the folks in Singapore, and they passed a law -- Singapore is a

city-state -- but they passed a law that said if an orphan drug is approved in the United States, we will allow it to be imported into Singapore, and it is hence approved. I think they've gone further with their law since then, but it was the first country other than the U.S. to acknowledge orphan "drugdom".

Europe was beginning to have meetings about orphan drugs, the first one being convened by a journalist who was very interested in orphan drugs, whose name was Michel Salamón,

Mr. Salamón, in addition to myself, brought a man by the name of Jean-Louis Alexandre, to the meeting. Jean-Louis was head of the French medicines agency or French FDA. Professor Alexandre began to agitate for an orphan drug act in Europe.

Also at that time, Japan became interested in an orphan drug act, and a physician in Osaka began to write about the need for an orphan drug act in Japan. I was invited on a couple of occasions to meet with Japanese hierarchy, so in 1993 the Japanese passed the second orphan drug program in the world. It is different than the U.S. program. It has as a population cutoff of 50,000 people in Japan, roughly equivalent to half the prevalence of a population in the U.S. to qualify to be an orphan drug.

SJ: And less ethnically diverse too.

MEH: Oh, far less ethnically diverse.

They had 10 years' exclusivity, we had seven years' exclusivity.

Ah, I forgot to mention a very important incentive of the Orphan Drug Act that has to go back to the previous area, and that is that there was seven years' exclusive marketing for that drug for that indication for every orphan drug that is approved, and many of these orphan drugs were either not patentable or off patent. It was the 1985 amendments that took away the requirement for non-patentability.

So now Japan had an orphan drug act. Some of the differences were 10 years' exclusivity versus our seven; a lesser prevalence; and they give their grants virtually exclusively to industry, we give ours primarily to academia.

TAPE 2, SIDE A

MEH: Our office never developed a good relationship with Japan. We didn't have a bad relationship with them. We just didn't have a relationship with them. Part of the reason was the Internet wasn't as big as it is today;

there's a 12-hour time difference; there's a significant language difference and none of us speak Japanese, and few Japanese spoke English; and they changed the Director of their program every two years as a matter of policy in all their health programs. So, as a result, we never developed a good relationship. Only now is that relationship really coming to fruition.

So we had first Singapore in about 1991; then Japan in 1993. Meanwhile, the Europeans are still discussing what they're going to do, and I am going back and forth on a fairly regular basis to Brussels or other meetings where prototypes of orphan drug programs are being discussed.

In 1998, at about seven o'clock one evening, I was sitting comfortably at my desk trying to finish up for the day, and the phone rang and I answered it, and a very British-sounding voice was on the phone. It turned out that it was the head of Australia's Therapeutic Goods Administration, Terry Gray. He was very interested in signing a "Memorandum of Understanding" (MOU) with the U.S. and developing an orphan drug program in Australia, would I come over and meet with them. I was delighted to do so, and was able to address some members of their Parliament. They had a press conference in their Parliament concerning

orphan drugs, to which I spoke, and they developed an orphan products program.

SJ: That's interesting.

MEH: There are photographs of us signing that agreement.

SJ: If you will get it to us, we will put it in the corridor project.

MEH: I will, but they're small pictures.

SJ: They can be enlarged and worked with.

MEH: That program in Australia, we've always had very good interaction. But they have a prevalence of fewer than 2,000 in the entire population. The population of Australia at that time was 20 million, so, 2,000 in that population is a very small number. And they have a program that still limps along. They were very concerned about the cost of some orphan drugs, which was an issue that was being raised at that time.

And then finally, in 1999, Europe passed their orphan drug regulation. It is a regulation and not legislation. In the process of developing that regulation, one of the questions that came up was the number of people that should be covered. The European Union (EU) was just coming into being, and they were looking at a finite number, for prevalence, they had 15 member states. And as their

consultant, I said to them, "Wouldn't you rather have a ratio of one to whatever, because I suspect you're going to be adding member states, and so your population will grow, and unless it is easy to amend a regulation like this, I think you would be better off doing it as a ratio," which is what they did, five per 10,000 or one per 2,000 in the population, which is more generous than Japan but less generous than the U.S. The U.S. is the most generous of all nations in their Orphan Drug Act as far as prevalence in the population is concerned. Australia is the least generous, and the rest fall in between.

The EU went online in the year 2000 -- and their program has done extraordinarily well, and there is very excellent back and forth discussion between the U.S. and the European program. They are moving rapidly in developing guidelines for small clinical trials and in working together with the U.S. on what is and what is not a disease. In other words, is lymphoma one disease or is there non-Hodgkin's lymphoma, spindle-cell lymphoma, and other kinds of lymphoma. The U.S. & EU try to get some parallelism and good transparency between decisions in the U.S. and the EU. So that has done well.

And then, since then, many other countries have developed orphan drug programs. Taiwan has an active

program; China is talking about one; some of the states in India are talking about programs; Mexico has talked about a program; Israel was rapidly moving toward a program. I do not know where that stands right now.

It's an idea whose time had sort of arrived as more and more programs came online.

So then if we go back and look at some of the diseases that have been well served by the orphan products development program, Suzanne mentioned AIDS. AZT was approved in 1986. At the time that it was approved, it had no patent, and the AIDS population -- it wasn't called AIDS then; it was called severe ARC, AIDS Related Complex. AIDS was not the predominant name that was used at that time. But the AIDS population was around 6,000, and the orphan products program assisted in the development of many of the early AIDS drugs to treat AIDS, and for many, many of the drugs that treated the opportunistic infections that occurred with AIDS. Pneumocystis pneumonia, which is a fairly common disease with AIDS, but it was still well under 200,000 for a long, long time; and then things like cystercercosis.

SJ: Would Kaposi's sarcoma have qualified for orphan status?

MEH: Yes. It would have qualified for orphan status prior to AIDS, and it qualified for orphan status for a long time with AIDS.

Kaposi's sarcoma used to be a disease that occurred mainly in older Italian men living south of the Po River. I do not know why.

I've always loved factoids, so I could remember that sort of thing.

Maybe -- and I don't mean to trivialize orphan diseases, but I really liked dealing with the obscure, the underserved, the unusual, those that no one else paid attention to, all of that, and I think that's what grabbed me about orphan drugs. That's probably why I liked the Indian Health Program so much. And in my training program in hematology, I worked with sickle cell disease and other unknown hemoglobins. So that's the niche that I have always found for myself.

So, anyway, AIDS was benefited significantly by the orphan drug program, and without patentability -- now, Burroughs-Wellcome, who developed AZT, later got a use patent for AZT but did not have one at the time that their drug was approved. Erythropoietin was not patentable. It had been first synthesized in 1957. That synthesis was published, and so as a compound, it was not patentable.

Now, Amgen has gotten many patents for it, but not a product patent. And they needed the Orphan Drug Act in order to be able to bring that product to market.

Human growth hormone was one of the early orphan drugs, and it was also one of the first biotech drugs. The orphan drug program has been touted as being a major assist to the development of biotechnology in the U.S. Biotech drugs were hard to patent initially. And so the Orphan Drug Act offered the kind of exclusivity that was necessary to give personal property protection for these products.

So you're looking at -- let's see, I might have to look at a list -- but certainly human growth hormone. Then there was Ceradase, which was initially made from human placentae, and then made by biotech methodology and approved as Cerezyme by Genentech; and a whole host of others that I can take a look at a list of orphan drugs.

RT: I think in some information you gave us on presentations you've made, you apparently made a point of talking about therapeutic foods. Does that relate at all to this orphan concept?

MEH: Yes, it does. There is no such thing as an orphan medical food, but there are primarily children with orphan diseases, rare diseases, who require certain foods for a proper and normal life. So, for instance,

phenylketonuria, these children have to consume a diet without an amino acid called phenylalanine, and if you look on the side of many of your foods, it will say either "not suitable for phenylketonuria," "contains phenylalanine," may say "does not contain phenylalanine."

One of the early grants that the Office of Orphan Products gave was to a group that were developing foods that looked like foods for kids with PKU, which is what phenylketonuria is called. And they were developing things that looked like hotdogs or birthday cake or doughnuts, because otherwise these children had to consume a liquid diet for their entire life. And when they reached pre-teen to teen years, they developed the normal rebellion of a normal kid and wanted to have hotdogs and hamburgers and other "forbidden foods. As a result, they developed mental retardation. These children did have some mental retardation to begin with. There is now an orphan drug called Kuvan, -- which it treats these kids so that they can eat a much more liberalized diet.

There is also special diets for kids with maple-syrup urine disease and with some of the other diseases of the urea cycle disorder. Some of those have received grant support to develop special foods or formulae. But there is

no well-defined orphan medical food nor are there any special programs other than the grants program.

RT: But those are still under the purview of the Office of Orphan Drug Products (OODP)?

MEH: If it's a grant. But if it's a grant, yes, the grant would be under the purview of the office. CFSAN, the Center for Food Safety and Applied Nutrition, looks at the particular infant formula or those are exempt infant formulas. In other words, they do not contain all the nutrients necessary for normal infants.

SJ: There aren't that many nutritional diseases either, are there?

MEH: There aren't that many nutritional diseases, diseases for which nutrition is the key to treatment. Yes and no. You know, diabetes is a very frequent disease for which nutritional management can help in large part for a number of people. It is not a nutritional disease, however.

SJ: But we've always been involved in that for artificial sweeteners and things like that.

MEH: Right, right, right. And there are a number of fad-diet things, too, that we wanted to stay away from as far as we could.

TAPE 5, SIDE A (tapes 3 and 4, sides A&B are blank)

SJ: We are here at White Oak campus on March 13, 2012, to continue our oral history interview with Marlene Haffner. We had so much going on the last time that we wanted to come back and pick up from where we left off.

We talked last time about the concept of orphan products as it grew from the U.S. to the EU in a way that you made possible, even though that was sort of beyond our mandate in the beginning, and that's probably one of your lasting legacies. It's sort of an early example, I guess, of global cooperation. Did you see it that way?

MEH: Absolutely, absolutely. And it wasn't just the E.U. I mean, the EU was late, because before the EU, there was Japan and there was Australia, and there was EU, and then there was Taiwan, and those are the ones in which I was involved.

SJ: Today, I would like to ask you about any tensions over the approvals of these orphan products, because your office, of course, was and is in the position of being the liaison and somewhat of an advocate to make sure that FDA gets the information that they need both about the disease and about the scientific work that was backing that.

MEH: Right.

SJ: These products don't go straight to the Center for Drug Evaluation and Research (CDER) or Center for Biologics and Research (CBER) without your input.

MEH: Oh, no. We're a translator.

SJ: Exactly. And so I know there were some tensions on certain products and certain things, but I'd love to hear you talk about them a little bit.

MEH: Do you mean tension between us and CDER or . . .

SJ: Well, no. Did you have any problems in terms of understanding what the standards would be?

MEH: No. Companies frequently had problems understanding what standards could be.

SJ: And were you the ones that talked to the companies?

MEH: We did a lot of talking to the companies. In fact, the review divisions said many times they were very happy that we were around because we took some of the workload off of their shoulders in two ways. One, we did explain standards, and the orphan products go through the same development process as do non-orphans; and that just because you were an orphan product, by no means did you get any special deals as far as development is concerned.

SJ: And there were companies that expected that since they were an orphan, they just didn't have to do the same kind of work. Did they equate that with expedited approval as well?

MEH: They equated it, not with FDA's expedited approval, we are an orphan and therefore we deserve whatever. And some of them even tried using a congressional route.

SJ: Do you remember any specifics?

MEH: I do. One of them is sodium phenylbutyrate, used for the metabolism amino acid.

The developer of that product simply did not wish to understand that . . . The developer just didn't want to understand that he had to do well-controlled trials, be they blinded or not, and not all drugs go by blinded trials. And he had a very good product that he had developed but that, quite frankly, needed validation and needed CMC and needed all the other things necessary for FDA approval.

SJ: CMC?

MEH: Is "chemical medicinal controls". But that product did not have CMC's. Ultimately what we did was found a sponsor to purchase the product from him, develop

it, get an FDA approval, and then it was sold to a third company, who continues to market the product to this day.

But that entailed a lot of explanation on our part to the original sponsor, and, quite frankly, some discussions with the division about what we were going to be able to get based on the fact that the population was extraordinarily small, the sponsor was not particularly cooperative but that this was a lifesaving product, and we succeeded.

SJ: But did Congress get involved?

MEH: No. Congress just didn't take the bait.

SJ: Do you have an example of when Congress did take the bait?

MEH: No. Congress never got involved in our program. There was never an oversight hearing. There was one hearing held by Senator Metzenbaum (Ohio), when he was in the Congress, over the price of orphan drugs, particularly, in two scopes: one, the price of orphan drugs, period; and, two, the price of an orphan drug following it coming off it being on a treatment Investigational New Drug (IND). For a treatment IND, you're not allowed to charge other than recovery costs, and then once the approved IND, the manufacturer or the sponsor obviously had to raise the price, Mr. Metzenbaum was concerned that that was too great

a price. But that was not a hearing in which the Office of Orphan Products was involved at all.

In fact, we did have one Office of Inspector General (OIG) look-see, particularly at the grants program, and I was very concerned when they told me that they were ready to come in and discuss their final report. And I said, "Hey, wait a minute. Don't we get to see a preliminary first?"

They said, "Trust us," and I thought, hmm, all right. And lo and behold, their final report said, "This is a very well-run program and we have no substantive comments or suggestions."

SJ: That is certainly uncommon.

MEH: Well, I've never heard of something like that. I was absolutely flabbergasted, astounded, and delighted. So I guess we were doing the program right.

SJ: And Congress, of course, got copies of that report in triplicate.

MEH: Yes, yes, yes, yes. I even took a copy of that report home with me, I think. I was rather proud of that, that they gave the program an absolute green light.

The orphans program was remarkably uncontroversial, other than what continues to this day: price. Not all orphan drugs are expensive, but some are, and in a report

last year -- I'm sure it's come out again this year, but I haven't seen it yet -- something like the top four most expensive drugs in the world were orphan drugs. But you have to understand that orphan populations are small populations; they wouldn't be orphan otherwise. And especially in our world of development of biologics and biotech, these are expensive drugs to make and to maintain. So they're going to be expensive. However, they are often cutting-edge and lifesaving.

SJ: Do you recall any other examples of drug disputes in the orphan field?

MEH: I don't remember the name of that drug. The disease is something pigmentosa, and I don't remember the drug and I don't remember that it was that close to any approval. But it's possible that something like that would come in and that we wouldn't know about it because there's never been a requirement that our office continue to be involved.

We always recommended to a sponsor that if they were coming in for a meeting with FDA for any reason, that they invite us as well, the rationale being not that we'll say much at the meeting with the sponsor, but at the pre-meeting there's always good discussion about here's what they want, here's what the situation is, and we could

sometimes weigh in and say, "Yes, but this population is in this situation, and there's only 20 patients in the U.S.," or even if it were only 2,000. So that would sometimes be helpful.

I don't remember the one to which you referred.

SJ: Do you remember any others that you thought were particularly compelling?

MEH: Well, one of the drugs that created, that took an awful long time to finally get approved was that of gamma-hydroxybutyrate for narcolepsy. Gamma-hydroxybutyrate had been around for a long, long time, it had been around since prior to the passage of the Orphan Drug Act and may even have been one of the drugs that was testified about at the time there were hearings about the Orphan Drug Act.

Gamma-hydroxybutyrate, unfortunately, also became known as the date-rape drug. It was very easy, I gather, to make in a home brew. It is important to note that never was the pharmaceutical-grade drug abused. It was only home-brewed drugs that were abused.

However, having said that, the Drug Enforcement Agency (DEA) became concerned and involved, as did many state legislatures, and they wanted to schedule this as a Schedule I, they wanted to ban it, they wanted to, you name

it, they wanted it not to be used, It took a large amount of negotiating on the part of our staff to keep it in such a fashion that it could be adequately studied and ultimately approved. It is approved. I think it's a Schedule III. It's got more strings attached to it than thalidomide does. It works very well for patients with narcolepsy, and I think it's also been approved for cataplexy.

But that was a very difficult, longstanding situation, and there were those in the Review Division that didn't want to approve it either, that it had too high a potential for abuse even though whatever abuse that had been seen, like I say, had not come from the pharmaceutical-grade product.

SJ: In pharmaceutical grade and elsewhere, but DEA doesn't have to worry about the pharmaceutical-grade?

MEH: DEA has quit their worrying. It does not seem to be the date-rape drug du jour right now and they're out worrying about something else.

SJ: You mentioned thalidomide, and the approval of the drug Thalidomid decades later while you were at FDA.

MEH: The first approval of thalidomide was an orphan drug.

SJ: Were you involved in that?

MEH: Absolutely. That was kind of exciting because that was approved for a side effect that occurs with leprosy called erythema nodosum leprosum, a very painful eruption mainly on the lower extremities, although it can exist elsewhere in the body, in patients that are being treated for leprosy. Thalidomide had been kept out of the U.S. market by Frances Kelsey, for which she got the Presidential Freedom Medal, I believe. And it was discovered that it had other very beneficial uses.

So then the question was how to bring it to market, and would we ever get over the stigma of thalidomide. Needless to say, no one wanted anyone that was potentially becoming pregnant to take thalidomide because of a known teratogen to unborn infants in the first trimester.

So we and the Review Division worked with the thalidomide survivors group to discuss with them what they thought about it. They felt strongly that the drug, if it had a good use, should indeed be approved, and it was. It has a very low usage because there aren't many patients in this country with leprosy. I don't know what its regulatory status is outside this country.

As far as I know, no patient has become pregnant while taking thalidomide. There are stiff regulations around its use, including the use of two birth-control measures by

women, and it's done well. And a variant of it has been approved for use in patients with multiple myeloma. So it's a drug that started out with a very sordid history that has gone on to be a useful product which can be used safely when appropriate safeguards are established around it.

SJ: I remember being at NIH when they had a large meeting, with FDA primarily, and you could feel the tension in the room. FDA staff themselves were concerned about what would happen.

MEH: We were all worried about it, needless to say. It was scary, and, yet, it was needed, and so how best to approach this.

Now, in actuality, it causes fewer birth defects than does Accutane, but that's not the point. Accutane was already in the market. This was not, and we were looking at prevention.

SJ: I seem to remember that there was an orphan indication for its use in AIDS wasting condition, of wasting during AIDS. Do you remember anything of the sort?

MEH: No. There are a number of drugs that are used for AIDS wasting, but I don't remember that thalidomide was one of those.

SJ: It was not submitted on that basis.

MEH: Well, they could have if they tested it, and it would not have had the same danger for fetal defects, at least as it was used in men. Now, it could have had those problems in women.

Well, there actually were a couple of other interesting things.

Lilly wanted to get orphan drug designation for a product -- an aromatase inhibitors -- to be used in patients as a prevention for breast cancer in postmenopausal women who were at high risk of developing breast cancer. The product was already in the marketplace and approved for osteoporosis. They wanted to get it designated as a prevention for breast cancer on economic grounds. Now, orphan products have a threshold of 200,000 people, fewer than 200,000 people in the U.S., or a product that will not be profitable for seven years. Lilly said this product would not be profitable for seven years because their other drug already had a price point, so they couldn't change the price for that indication, and it was about to go off patent. So after extensive review and discussion, and discussion with general counsel and further review, and discussion with the company, and back and forth, we decided to go ahead and designate it.

I thought it was a very exciting designation because it was for prevention. It is very hard to obtain drug approval, be it an orphan or not, for prevention as you are looking for something that does not happen. That requires, quite frankly, very large clinical trials.

The Lilly drug has been approved. It was approved as an orphan. I don't remember how many years ago. And I thought it would get a lot of press. It did not. Lilly decided not to make much hay out of it. But I still think it was a very exciting approval.

SJ: Now we did want to talk some more about some of the cutting-edge orphan drug work. For example, you were talking about the fact that orphan products brought a biostatistical challenge to the forefront in evaluating small clinical trials . . .

MEH; Well, it was difficult for some orphan products. The European Union issued a white paper on clinical trials for small-prevalence diseases.

SJ: Around when?

MEH: Oh, my. Probably 12 years ago, 15 years ago.

SJ: The late '90s?

MEH: Yes. Oh, no, no. I think it would be the year 2000 or thereabouts. It's on their website. We can get it.

But the point is that they were beginning to look at it. I think FDA has looked at it in greater detail, and, indeed, that effort came from the Office of Orphan Products. And it came to fruition out of the Office of Orphan Products. And yes, you're seeing more and more trials for small disease, small-prevalence diseases, these days.

Looking back, pegylation, which is now fairly common, was first used in an orphan product. It's adding polyethylene glycol, called PEG, to a compound, which makes it possible for that compound to enter the cell. And prior to that, it was difficult, if not impossible, to get a drug to operate intracellularly. But for adenosine deaminase deficiency, this was a Ph.D. thesis or a Ph.D. study. Abe Abuchowski learned how to pegylate adenosine deaminase, and it was then taken up by the cells. The cells could operate normally in these children who had SCIDS, Severe Combined Immunodeficiency.

SJ: Bubble boy?

MEH: Bubble-boy disease, bubble-girl disease, bubble whatever. Children with the disease could then lead far more normal lives, and many of these kids are graduating college today.

TAPE 5, SIDE B

SJ: Okay. So, we were talking about some examples of, we were talking about cutting edge work related to orphans.

MEH: Well, liposomal encapsulation was first used by orphan drugs. That means coating the product or coating the capsule of the product with liposome, a fatty material. It has been used in a number of orphan products to enhance their effectiveness, particularly liposomally coated encapsulated L-asparaginase for use with acute leukemias of children and some of the antifungal products, particularly in cases of people that are debilitated that develop overwhelming fungal diseases. And then there's other applications as well. But it was first used in orphans. What else was first done in orphans? One of the orphan grants was given to a researcher who was looking at treatment of those patients who are born without the ability to make cholesterol. Most of us wish we made less cholesterol. But we do need some cholesterol, and for the children that are born without the ability to metabolize cholesterol at all, they will die without it. That particular grant gave way to the development of the statins because it was by understanding cholesterol metabolism that

the development of the statins to lower cholesterol was discovered. So there's some neat stuff that's come along.

Today, the first gene therapies are being used, being trialed in patients with orphan diseases. So, you know, orphans lead to exciting cutting-edge development.

SJ: What kinds of successes have we witnessed? In gene therapy, for example?

MEH: We have none that we can refer to. I think we will have some. Initially, some of the problems with the insertion of genes was that some of these -- and they were all children -- went on to develop malignancies, generally leukemias. I also think most of those leukemias could be treated. But that's not a side effect that one necessarily wants, and so they're looking at new ways and new vectors to make gene insertion safer.

SJ: You mentioned cholesterol disorders. Did you have any role in advising filmmakers during the production of "Lorenzo's Oil" - the film that certainly brought the issue of orphan drugs and FDA approval to the attention of the public in 1992.

MEH: The movie "Lorenzo's Oil" was made about a disease called adrenoleukodystrophy, and had to do with a drug that is a combination of two oils which will lower very-long-chain fatty acids. The trouble is it lowers it

well in the peripheral blood, but it needs to get across the blood-brain barrier. But that particular movie was about a little boy, who died only a year or so ago, with adrenoleukodystrophy, and Dr. Hugo Moser, one of our grantees for a long time, was developing this product. He discerned that it simply was not working. The family did not want to believe that, and in the movie Dr. Moser is depicted as an ogre. He was anything but. He has since died. But it was an interesting movie. The father came to me, the father of the little boy came to me long after and said, "You know, I made a mistake." It was a well-received movie with Susan Sarandon and Nick Nolte, and all of us in the Office of Orphan Products Development took an afternoon and went to see the movie, because we were sure we would just be bombarded with questions. Quite frankly, I don't think we got any.

SJ: It certainly brought orphan products to the minds of the public in a way that I don't think had ever happened before.

MEH: It did.

SJ: It showed clearly how much ones hopes can dictate a lot of what is seen by patients and practitioners alike.

MEH: Absolutely.

SJ: Did Lorenzo live anywhere near a normal life?

MEH: Oh, no, no, no. He was severely mentally . . .

SJ: But in terms of longevity?

MEH: No. He died at the age of 21.

SJ: And that would have been predicted without treatment?

MEH: He would have died earlier without it, but he lived basically in a family-derived ICU, so I don't think that his life was made any longer even with that level of care. He certainly didn't lead a quality of life.

SJ: Can we talk now a little about the grants program for orphan products? How was it set up? What has it accomplished?

MEH: The grants began in 1983 with \$500,000. Today, 30 years later, it is only at \$14 million and has been at that amount for a long, long time so that, in essence, the amount of dollars it can award has been significantly eroded. But it's been a very successful program, and were there more dollars available for it, I think one could see a lot of return on investment.

It is patterned very much around the NIH grant process. There is an annual request for applications that is issued. There were, for a while, two closing dates, but that turned out to be more trouble than it was worth. So

there's one closing date, and mainly academic researchers apply. All of the grants have to be for clinical trials; it cannot be pre-clinical. I would have loved to have money for pre-clinical trials because that's a lot of where there is a big gap in the development of products, but we didn't have enough money and the law said clinical, therefore . . .

SJ: Yes. Let me just make sure. The grants are given through Health and Human Services (HHS)?

MEH: The grants are coming through HHS and through the regular budget for FDA? It comes through the regular FDA budgeting process.

SJ: As opposed to the regular appropriations process.

MEH: Right. This is not an NIH program. There are no NIH dollars. Nor does it come directly through the Orphan Drug Program, but comes from just regular FDA appropriations. And each year we would like to have FDA request more in the budget, but it always loses out. But it's a shame because there have been some very nice projects that have ultimately reached approval from that, and many of those projects would probably never have gotten into humans in the first place had it not been for that grants program.

That grants program also funds what one called orphan devices. We didn't have a definition, but the regulations surrounding the grants program allows those grants to be used for medical devices, drugs and biologics, and medical foods, all of which to be used in orphan indications.

So the first product that was approved that had received orphan grant support was a very interesting angioscope which could look into arteries and could, for patients that had large pulmonary thrombi, remove them. And patients would be carried into the hospital sitting bolt-upright, barely able to breathe, and be able to walk out because the product could be used so effectively. That's exciting.

There have been medical foods that have been studied. Kids with phenylketonuria, PKU, must all their lives generally live on a formula which does not have phenylalanine in it, and somewhere around age eight or so, kids begin to rebel and they want to eat real food. Well, if they eat real food, they risk mental retardation. And this is a battle that every family with a kid with PKU has.

So, one of these grants looked at the development of things that looked like foods: hotdogs, birthday cakes, other things that kids would want.

SJ: And they're consumed in social situations.

MEH: That's right. And while I don't know how many of those phenylalanine-deficient foods are available for those youngsters, I think some are, and that was a result of that grant. Now, there was one researcher who was very annoyed with the program and said, "These people have to learn that they're going to live on formula for the rest of their lives, and that's the way it is." I didn't go along with that thinking. Anything is better than nothing, was my point of view.

SJ: He must not remember having an eight-year-old child.

MEH: Yes. I don't know whether he ever had an eight-year-old child.

And since its inception, some 40+ products have begun in the grants program and have ultimately received approval, in large part because of the money that the grants program was able to provide. So it's been quite successful. It could have been more successful had there been more grants money available, but there wasn't, and that's the way life is, or was.

I know they would like more money, and now that I'm not working for the government, maybe I can help them get some more money.

SJ: So, the government's "revolving door" isn't all bad then . . . Some former officials do leave and work to make an impact in needed areas. Correct?

MEH: Right. Yes, yes.

And let me just go on and say that the Request for Applications goes out, applications comes in, they're reviewed initially by the orphan products staff to make sure that they are in compliance with the RFA, the Request for Applications, and then they are reviewed by an outside panel of experts. So the review process is similar to, if not identical to, the NIH review process, but it's managed totally by the Food and Drug Administration.

SJ: As we're finishing up, is there anything else that you wanted to make sure that we cover in this interview and get on the record?

MEH: I guess one thing that I always found delightfully intriguing is, orphan products are very seductive. They're interesting. One's ability to assist in the development of products to adequately treat patients with rare diseases is very fulfilling. And I was privileged to work in an office where we had no turnover of staff. I mean, that was the good news and the bad news -- no one ever left unless they retired, and they didn't retire until they were well past retirement age or presumed

retirement age. And it was just fun to work in the program, fun meaning productive and interesting.

One of the things that I may or may not have mentioned is the unintended consequences of the Orphan Drug Act, and they're all good. I don't think that at the time that the Orphan Drug Act was passed and signed into law, anyone really had any comprehension of the breadth and depth of rare diseases and the drugs that ultimately could treat them. So we discovered in the process of designation and approval that somewhere between 85 and 90 percent of all orphan diseases were serious and life-threatening diseases. So we're talking about diseases like phenylketonuria where kids end up severely mentally impaired; similarly for ornithine transcarbamylase disease and some of the amino acidurias. We're talking about the acute leukemias, both of adults and childhood, which are certainly life-threatening and life-shortening. We're talking about many cancers because you think of cancer as very prominent, and overall it certainly is, but except for breast cancer, colon cancer, prostate cancer, and lung cancer all have a frequency of less than 200,000. But other than that, almost if not every cancer is an orphan disease. Pancreatic cancer, malignant melanoma. They all occur in fewer than 200,000 people in the U.S. And so researchers

looking at these diseases and therapies for them can look to the incentives of the Orphan Drug Act as incentives that will spur development of drugs for those diseases.

Another area is pediatrics. At least 50 percent of drugs for rare disease begin as pediatric diseases. They may go on to longer or they may be so life-shortening that they don't go on very long at all. But pediatric diseases are an important component of orphan diseases, rare diseases; therefore the drugs are an important component as well.

And the Office of Orphan Products has traditionally treated pediatric indications as a different indication than for a similar adult disease. Kids are not just little adults. Dosages can't just be cut in half or in thirds or treated based on age, but they have to be looked at because metabolism in children is quite different than is metabolism of drugs in adults. So I think that's what I wanted to say about that.

SJ: Very good.

END OF INTERVIEW

## ***CURRICULUM VITAE***

April 18, 2006

**NAME:** Marlene Elisabeth Haffner, M.D., M.P.H.  
Rear Admiral, USPHS

**ADDRESS:** (Home)



(Office)

Director, Office of Orphan Products Development (HF-35)  
5600 Fishers Lane Room 6A55  
Rockville, Maryland 20857  
Telephone: 301-827-3666  
Facsimile: 301-827-0017  
Internet Address: mhaffner@oc.fda.gov

**MARITAL STATUS:** Married to William H.J. Haffner, M.D., 1963

### **EDUCATION:**

Western Reserve University Cleveland, Ohio	1958-61 Chemistry Major
George Washington University School of Medicine Washington, D.C.	1961-65 Doctor of Medicine
Johns Hopkins University School of Hygiene and Public Health Baltimore, Maryland	1989-91 Master of Public Health Department of Health Policy & Management
Harvard University John F. Kennedy School of Government Cambridge, Massachusetts	August 1995 Program for Senior Managers in Government

### **Post Graduate Training:**

Internship (Medicine) George Washington University Hospital Washington, D.C.	1965-66
Fellowship (Dermatology) Columbia Presbyterian Medical Center New York, New York	1966-67

Residency (Internal Medicine) 1967-69  
St. Luke's Hospital, Columbia University  
New York, New York

Fellowship (Hematology) 1969-71  
Albert Einstein College of Medicine  
Bronx, New York

**CERTIFICATION:** American Board of Internal Medicine, 1972

**LICENSURE:** New Jersey (active) and New York (inactive)

**EMPLOYMENT RECORD:**

*Director, Office of Orphan Products Development  
Food and Drug Administration, Rockville, Maryland*

Dates Held - September 1987 -

BRIEF HIGHLIGHTS OF POSITION - As Director, Office of Orphan Products Development, FDA, responsible for leadership and management of the FDA orphan products development program. These responsibilities include coordination of FDA's scientific and regulatory activities associated with the development and regulation of orphan products, and administration of \$13.5 million in grants for pivotal clinical trials toward orphan product approval. The orphan products program influences, and is influenced by the regulated pharmaceutical industry, medical professional organizations as well as patient advocacy groups. Materially influences decisions associated with the research, development, and approval of designated orphan drugs and products, including biologics, medical devices, diagnostic products and medical foods. Has extensive relationships with academic institutions and individual researchers to assist in the development of products to treat small and exceptionally needy populations of people with rare diseases.

Maintaining sensitivity to the needs of special populations, is integrally involved with patient access to therapy for rare disorders where access may otherwise be limited because of financial or physical barriers. Responsible for the long and short range planning of the Office with an emphasis on the development of legislative initiatives for orphan products and rare diseases. Works cooperatively with groups within the European Union, Australia, and Japan in assisting them to develop programs similar to the U.S. Orphan Products Program.

***FDA Representative to the Office of the Surgeon General, USPHS  
Food and Drug Administration, Rockville, Maryland***

Dates Held - 1987 - 2004

BRIEF HIGHLIGHTS OF POSITION - Represents the Surgeon General to the FDA and the FDA to the Surgeon General on matters of PHS Commissioned Corps policy, including recruitment, retention, benefits, training, and career development. Provides FDA Commissioned Officers and program managers with necessary information regarding Commissioned Corps policy and initiatives. Meets on a monthly basis with other PHS OPDIV representatives to discuss and develop policies and initiatives essential to both the PHS OPDIVs and Officers. Coordinates Uniformed Services University of the Health Sciences (USUHS) activities for the FDA. Responsible for FDA medical student clerkships during summer and elective rotations. Serves since 1986 on the USUHS medical student Training and Assignment Committee. Chairs PHS Workgroup on 30-year Retirement and makes recommendations to the Surgeon General regarding changes to and implementation of policy. Serves as member of the USUHS F. Edward Hébert School of Medicine admissions committee representing the Surgeon General and the interests of the PHS. Serves several times a year as preceptor in USUHS Ethics in Medicine Courses.

***Director, Office of Health Affairs, Center for Devices and Radiological Health  
Food and Drug Administration, Rockville, Maryland***

Dates Held - July 1982 - September 1987

BRIEF HIGHLIGHTS OF POSITION - As Director, Office of Health Affairs, Center for Devices and Radiological Health, served as the principal medical advisor to the Center Director. Responsible for developing critical medical reviews in the decision-making process of the Center. Evaluated medical research data from within the Center, government, and private sectors. Developed and coordinated liaison programs with medical and allied health professional groups to promote better understanding of and support for FDA's medical device and radiological health programs. Was the principal national spokesperson for the Center and frequently for the FDA on matters of health with regard to programs of the Center, speaking as necessary on issues of concern to the public, such as the risk of Toxic Shock Syndrome in relation to the use of tampons.

***Associate Director for Health Affairs, Bureau of Medical Devices  
Food and Drug Administration, Rockville, Maryland***

Dates Held - July 1981 - June 1982

BRIEF HIGHLIGHTS OF POSITION - As Associate Director for Health Affairs, Bureau of Medical Devices, Food and Drug Administration, served as the principal medical advisor to the Bureau Director and responsible for developing critical medical opinions in the decision making process of the Bureau. Developed liaison programs with U.S. and foreign health professional organizations. Served as principal advisor on medical research and testing programs within the Bureau and with other FDA components.

***Director, Navajo Area Indian Health Service (NAIHS),  
Indian Health Service/HRSA/PHS, Window Rock, Arizona***

Dates Held - September 1974 - June 1981

BRIEF HIGHLIGHTS OF POSITION - As Area Director of the Navajo Area Indian Health Service administered a comprehensive medical care program which covered an area of approximately 25,000 square miles in the States of Arizona, New Mexico, and Utah and which included complete preventive, therapeutic, rehabilitative, and environmental health services. This health program was divided into 8 service units operating 6 hospitals, 10 general health centers, 4 school health centers and numerous clinics and health stations which served 150,000 Indians.

Duties were equivalent to the responsibilities performed by the local health commissioner of a large municipality. The Director was required to be responsive to all of the health problems and demands found in a health commissioner's sphere of responsibility including the cultural norms of the community.

***Chief, Department of Internal Medicine  
Gallup Indian Medical Center, Gallup, New Mexico***

Dates Held - August 1971 - September 1974

BRIEF HIGHLIGHTS OF POSITION - Served concurrently as Chief, Department of Internal Medicine, Chief, Adult Outpatient Department and Clinical Director of the Gallup Indian Medical Center, the largest referral hospital in the Indian Health Service. Was medically and administratively responsible for the medical management of more than 1,400 acute medical patients per year, and for supervising the medical care of more than 50,000 outpatients yearly.

***Chief, Adult Outpatient Department  
Gallup Indian Medical Center  
Gallup, New Mexico***

Dates Held - 1971 - 1974

BRIEF HIGHLIGHTS OF POSITION - Concurrent with Chief, Department of Internal Medicine

***Acting Clinical Director  
Gallup Indian Medical Center  
Gallup, New Mexico***

Dates Held - 1973 - 1974

BRIEF HIGHLIGHTS OF POSITION - Concurrent with Chief, Department of Internal Medicine

**ACADEMIC APPOINTMENTS:**

- |   |  |
|---|--|
| 2003- Professor, Department<br>of Preventive Medicine/Biometrics                                      | F. Edward Hébert School of Medicine<br>Uniformed Services University of<br>the Health Sciences (USUHS)<br>4301 Jones Bridge Road<br>Bethesda, Maryland |
| 2003- Professor, Department of Medicine   | F. Edward Hébert School of Medicine<br>Uniformed Services University of<br>the Health Sciences (USUHS)<br>4301 Jones Bridge Road<br>Bethesda, Maryland |
| 1995- Adjunct Associate Professor,<br>2003 Department of Preventive<br>Medicine/Biometrics            | F. Edward Hébert School of Medicine<br>Uniformed Services University of<br>the Health Sciences (USUHS)<br>4301 Jones Bridge Road<br>Bethesda, Maryland |
| 1995- Clinical Associate Professor,<br>2003 Department of Medicine                                    | F. Edward Hébert School of Medicine<br>Uniformed Services University of<br>The Health Sciences (USUHS)<br>4301 Jones Bridge Road<br>Bethesda, Maryland |
| 1985- Clinical Assistant Professor,<br>1994 Department of Medicine                                    | F. Edward Hébert School of Medicine<br>Uniformed Services University of<br>the Health Sciences (USUHS)<br>4301 Jones Bridge Road<br>Bethesda, Maryland |
| 1974- Clinical Assistant Professor,<br>1985 Department of Medicine                                    | University of New Mexico<br>School of Medicine<br>Albuquerque, New Mexico  |
| 1974- Clinical Assistant Professor,<br>1985 Department of Family, Community<br>and Emergency Medicine | University of New Mexico<br>School of Medicine<br>Albuquerque, New Mexico  |
| 1971- Assistant Clinical Professor,<br>1973 Department of Medicine                                    | Albert Einstein College of Medicine<br>Bronx, New York   |
| 1969- Visiting Assistant Attending<br>1971  | Bronx Municipal Hospital Center<br>Bronx, New York   |

**TEACHING EXPERIENCE**

- |  |   |
|--|---|
| 1990 - Mentor for PHS-sponsored<br>USUHS Medical Students  | F. Edward Hébert School of Medicine<br>Uniformed Services University of<br>the Health Sciences (USUHS)<br>4301 Jones Bridge Road<br>Bethesda, Maryland  |
| 1987 - FDA Preceptor for USUHS<br>Medical Students   | F. Edward Hébert School of Medicine<br>Uniformed Services University of<br>the Health Sciences (USUHS)<br>4301 Jones Bridge Road<br>Bethesda, Maryland  |
| 1985 - Instructor in Introduction<br>to Clinical Medicine I  | F. Edward Hébert School of Medicine<br>Uniformed Services University of<br>the Health Sciences (USUHS)<br>4301 Jones Bridge Road<br>Bethesda, Maryland  |
| 1982 - Preceptor, FDA USPHS<br>Commissioned Officer<br>Student Training and Extern<br>Program (COSTEP) | U.S. Public Health Service<br>Rockville, MD   |
| 1975 - Preceptor, Internal<br>1981 Medicine Residency<br>Program<br>(at Tuba City, AZ)                 | University of California San Diego<br>School of Medicine<br>San Diego, California   |
| 1971 - Preceptor, Medical Student<br>1981 Programs, Navajo<br>Indian Health Service<br>facilities      | <i>Students participated from<br/>multiple institutions, including:</i><br>University of New Mexico<br>School of Medicine<br>Albuquerque, New Mexico<br><br>University of Pittsburgh<br>School of Medicine<br>Pittsburgh, Pennsylvania<br><br>Brown University School of Medicine<br>Providence, Rhode Island<br>HPSP Scholarship Program<br>Department of the Army |

**HONORS: / Professional Awards - Inside Government**

2003	USPHS Physicians Professional Advisory Committee's <i>Physician Executive of the Year Award</i>
2002	PHS Foreign Duty Award (FDA)
2000	DHHS Secretary's Award for Distinguished Service
1997	USPHS Distinguished Service Medal
1997	FDA Equal Opportunity Achievement Award (1987-96)
1993, 1996	Surgeon General's Exemplary Service Medal, USPHS
1986, 1993	USPHS Meritorious Service Medal
1993	Surgeon General's Medallion, USPHS
1989	USPHS Outstanding Service Medal
1985, 1998	USPHS Outstanding Unit Citation
1985, 1988, 1992, 1993, 1994, 1995, 1996, 1998, 1999 2000	USPHS Unit Commendation
1988	Commissioner's Citation, FDA
1988, 1989	USPHS Citation
1978	USPHS Commendation Medal
1976, 1980, 1988	USPHS Commissioned Corps Exceptional Capability Promotions (0-6, 0-7, & 08)

**Professional Awards - Outside Government**

2005	University Medal – Uniformed Services University of the Health Sciences (USUHS).
2002	American Academy of Pharmaceutical Physicians 2002 Special Recognition Award for Outstanding Contribution to Pharmaceutical Medicine.

- 1999 Richard A. Kern Award  
Association of Military Surgeons of the United States
- 1996 Robert Brutsche Award  
"For Exceptional Service to the Commissioned Officers Association of the  
United States Public Health Service."  
Commissioned Officers Association (COA)
- 1996 Outstanding Service to the Public Health Award  
"For Leadership and Commitment to the Orphan Disease Community."  
National Organization for Rare Disorders (NORD)
- 1992 "In Recognition of ... needs of persons with Hemophilia."  
National Hemophilia Foundation
- 1988 Award of Recognition  
National Organization for Rare Disorders (NORD)
- 1976 Presidential Citation  
National Environmental Health Association

***Academic Awards -***

Mortar Board Society, Western Reserve University

Kane King Obstetrical Society, George Washington University School of Medicine

Phi Delta Epsilon, National Journalism Honorary Society

Delta Sigma Phi, National Chemistry Honorary Society

***Other Recognitions -***

Distinguished Leaders in Health Care  
American Society in Biographical Research

Who's Who in Health Care  
Hanover Publications, Inc.  
New York, New York

Who's Who In Medicine  
Marquis Who's Who  
Chicago, Illinois

International Who's Who in Medicine, Second Edition

International Who's Who of Professionals

Who's Who in Medicine and Healthcare

Who's Who in America

Who's Who in the World

Who's Who of Emerging Leaders in America

Who's Who in the East

Who's Who in the West

Who's Who in American Women

Who's Who in Science and Engineering

The National Registry of Who's Who

**UNIFORMED SERVICES EXPERIENCE:**

Active Duty: U.S. Public Health Service (Regular Corps) - 3/1975 -  
Current Rank: Assistant Surgeon General/Rear Admiral 0-8

**COMMITTEE ASSIGNMENTS AND ADMINISTRATIVE EXPERIENCE:**

***Academic***

Admissions Committee, F. Edward Hébert school of Medicine, Uniformed Services University of the Health Sciences, representing the Surgeon General, USPHS, Bethesda, Maryland: 1986-

Appointments, Promotions, & Tenure Committee, F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences: 1995 - 1998

PHS USUHS Training and Assignment Committee, Office of the Surgeon General, Rockville, Maryland: 1992 -

Delegate of the Edgar Snow Memorial Foundation, Inc., to the People's Republic of China, University of Missouri School of Medicine, Kansas City, Missouri: 1981 and 1984

***Public Health Service/United States Congress***

Orphan Products Board, Assistant Secretary for Health, Department of Health and Human Services, Washington, D.C.: 1986 -

Consortium on Rare Diseases, Assistant Secretary for Health, Department of Health and Human Services, Washington, D.C.: 1991 -1997

National Commission on Orphan Diseases, United States Congress, FDA member, Washington, D.C.: 1987 – 1989

Special Emphasis Panel on the Coordination of Rare Diseases, Office of Rare Diseases, Office of the Director, National Institutes of Health, 1997 -

National Steering Committee of the Federal Credentialing Program (FCP): 1998 –

***International Consultant***

Australian Therapeutic Goods Administration -- Toward developing an Australian Orphan Drug Act; 1997- 2001

European Union -- Toward establishing orphan drug legislation within the European Community; 1994 – 1999

***Office of the Surgeon General***

USPHS Bicentennial Committee: 1994 - 1998

USPHS Visioning Committee: 1994 - 2000

Retirement Work Group, Office of the Surgeon General, Rockville, Maryland: 1990-1993  
Chair: 1990 - 1993

Physician's Professional Advisory Committee to the Surgeon General, USPHS, Rockville, Maryland: 1982 - 1988  
Chair: 1984 - 1988

Consultant to Division of Beneficiary Medical Programs, Office of the Surgeon General, Rockville, Maryland: 1986 -

USPHS Commissioned Corps Centennial History Committee, Rockville, Maryland: 1988

***Public Health Service Commissioned Corps Boards***

PHS Exceptional Capability Promotion Board: 1989, 1990

PHS Flag Officer Billet Board: 1989, 1990-1992, 1996-  
Chair: 1997 - 2001

PHS Flag Officer Promotion Board: 1989 - 1992; 1996 - 2000

PHS Retirement Board: 1989 – 1996  
Chair: 1993 – 1996

***Food and Drug Administration:***

Food and Drug Administration Coordinator on Department of Health and Human Services Leadership Team for *Healthy People 2010*: 2000 – 2003

Health Objectives of the Year 2000, Laboratory Initiatives Task Working Group, Centers for Disease Control and Prevention, Atlanta, Georgia: 1990 - 1997

PHS Crisis Management Team, Rockville, Maryland: 1992 –

Pharmaceutical Manufacturers Association (PMA) Commission on Drugs for Rare Diseases, FDA representative, Washington, D.C.: 1986 - 1995

Center for Devices and Radiological Health Research Involving Human Subjects Committee, FDA IRB, Rockville, Maryland: Chair 1981 - 1987

FDA International Visiting Scientists Committee, FDA, Rockville, Maryland: 1981 - 1982

***Indian Health Service***

Council of Indian Health Service Area Directors, Indian Health Service: 1974 - 1981  
Chair: 1980 - 1981  
End Stage Renal Disease Policy Committee: 1976 - 1980

Patient Care Data Committee, Indian Health Service: 1975 - 1981  
Chair: 1978 - 1981

Bicentennial Advisory Committee to the Navajo Nation, Indian Health Service, Window Rock, Arizona: 1974 - 1977

Navajo Nation Area Health Education Committee (AHEC) Board of Directors, Indian Health Service, Window Rock, Arizona: 1974 - 1981

Navajo Nation Health Foundation Board of Directors, Indian Health Service, Window Rock, Arizona: 1974 - 1981

Executive Committee, Gallup Indian Medical Center, Indian Health Service, U.S. Public Health Service: 1971 – 1974

***Other Health Professional Organizations***

Fellowship Diploma, the Royal College of Physicians, London, England – 2005

Food and Drug Administration Coordinator on Department of Health and Human Services Leadership Team for *Healthy People 2010*: 2000 – 2003

American College of Physicians Clinical Practice Subcommittee, American College of Physicians, Philadelphia, Pennsylvania: 1990 -1991

United States Pharmacopoeia Family Practice Advisory Panel, USP, Rockville, Maryland: 1985 – 1990

Task Force on Consensus Review of the Physicians Office Laboratory Guidelines, National Committee for Clinical Laboratory Standards (NCCLS), Philadelphia, Pennsylvania: 1987 -

Subcommittee on Clinical Evaluation of Tests, National Committee for Clinical Evaluation of Tests (NCCLS), Wayne, Pennsylvania: 1983 - 1995

Committee E Thermometry, American Society for Testing and Materials (ASTM), Philadelphia, Pennsylvania Committee E Thermometry: 1985 - 1987

## **BOARD MEMBERSHIP:**

### ***Health Professional***

Anesthesia Patient Safety Foundation, Board of Directors, American Society of Anesthesiology, Chicago, Illinois: 1985 - 1988

Board of Directors, Chronic Disease Society, Minneapolis, Minnesota: 1993-1996

National Sjogren's Syndrome Association Associate Advisory Board, Phoenix, Arizona: 1993 -

Children's National Medical Center Children's Research Institute Board of Directors,, Washington, D.C: 1998 -  
Vice Chair & Chair-elect: 1999-2000  
Chair: 2001 -

### ***Other Professional***

Johns Hopkins University School of Hygiene & Public Health  
Dean's Alumni Council: 1995 -

Johns Hopkins School of Hygiene and Public Health Alumni Association  
Vice-Chair Washington Chapter: 1993 - 1995  
Executive Committee: 1993 - 2002  
Chair Washington Chapter: 1995 - 2002

Commissioned Officers Association, Board of Directors: Washington, D.C.  
Elected as Member-at-Large: 1983 - 1989  
Vice Chair: 1984 - 1985  
Chair: 1985 - 1986  
Chair, Annual Meeting and Education Committee: 1988 -  
Search Committee, COA Executive Director: 1994-1995

Association of Military Surgeons of the United States, Representing the Office of the  
Surgeon General, Rockville, Maryland:  
Annual Core Program Committee: 1985 - 1991  
Chair, Core Program Committee: 1987  
Chair, Nominations Committee: 1992 -

**Editorial Board**

*Modern Drug Discovery* Editorial Advisory Board; 1998 -

**SOCIETIES:**

American College of Physicians: Member 1973 - 1977; Fellow 1977 -  
Clinical Practice Subcommittee 1990 - 1991

American College of Clinical Pharmacologists: 1972 -

American College of Physician Executives: 1994 - 1996

American Public Health Association: 1982 -

American Medical Association: 1982 -

Chronic Disease Society, Board of Directors, Minneapolis, Minnesota: 1993 - 1996

Commissioned Officers Association: 1974 -  
Board of Directors: 1983 - 1989  
Vice-Chairperson: 1984 - 1985  
Chairperson: 1985 - 1986  
Insurance Committee: 1983 - 1989  
Field Concerns Committee: 1989 - 1992  
Liaison to Navajo Area Branch: 1983 - 1989  
Liaison to Albuquerque Branch: 1983 - 1984  
Chair, Meeting and Education Committee: 1988 -  
Co-Chair, Annual Meeting Scientific Program Committee:  
1994, 1995, 1996, 1997, 1999, 2000, 2003, 2004

Anchor and Caduceus Society (Historical Society of the USPHS): 1992 -

Regulatory Affairs Professional Society: 1990 -

Association of Military Surgeons of the U.S.: 1982 -  
Annual Core Program Committee: 1985 - 1991  
Chair, Core Program Committee: 1987  
Chair, Nominations Committee: 1992

National Military Families Association 1995 -  
Board of Governors 1996 - 2000

**PUBLICATIONS:*****Refereed***

Stephen J. Kunitz, M.D., Ph.D., Helena Temkin-Greener, Ph.D., David Broudy, M.S., M.P.H., & Marlene E. Haffner, M.D., F.A.C.P. Determinants of Hospital Utilization and Surgery on the Navajo Indian Reservation. *Soc. Sci. & Med.* Vol. 15B, 1981:71-79.

Helena Temkin-Greener, Ph.D., Steven J. Kunitz, M.D., Ph.D., David Broudy, M.S., M.P.H., & Marlene E. Haffner, M.D., F.A.C.P. Surgical Fertility Regulations Among Women on the Navajo Indian Reservation: 1971-1978. *American Journal of Public Health*. Vol. 71, No. 4, April 1981:403-407.

Marlene E. Haffner, M.D., Dixie Farley. Health Fraud: A Growing Problem. *Military Medicine*. July 1986, Vol. 151:374-379.

Marlene E. Haffner, M.D. The FDA's Interim Rule for Expedited Development and Approval of Drugs for Life Threatening Illness: Orphan Drug Designations. *Regulatory Affairs*. Vol. 1, Fall 1989:201-207.

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Twenty Years of the Orphan Drug Act; Federation of Italian Rare Diseases (UNIAMO); Venice, Italy, September 2002.

Emerging Therapies in Orphan Products; 29<sup>th</sup> Annual Meeting Japanese Society of Pediatric Clinical Pharmacology; Tokyo, Japan, September, 2002.

Twenty Years of the Orphan Drug Act: What it Means to You; 3<sup>rd</sup> Annual World Congress & Exposition on Disabilities; Orlando, FL, October 2002.

Research & Development of Emerging Therapies for Rare Diseases in the U.S.; EPPOSI Workshop, Partnering for Rare Disease Therapy Development; Rome, Italy, October 2002.

Focus on Orphan Drugs Provisions-Differences Across Continents; Scripps Clinic & Bio, 5<sup>th</sup> Clinical Development Symposium; La Jolla, CA, February 2003.

Biological Similarity & Equivalence: Same vs. Different; Scripps Clinic & Bio, 5<sup>th</sup> Clinical Development Symposium; La Jolla, CA, February 2003.

Controlled Drug Distribution/FDA Post-Market Conditions; Scripps Clinic & Bio, 5<sup>th</sup> Clinical Development Symposium; La Jolla, CA, February 2003.

Using Information Technology to Meet FDA's Regulatory Mission; BioIT World Conference & Expo; Hong Kong, February 2003.

Orphan Designation in the United States: FDA Perspective; Drug Information Association 15<sup>th</sup> Annual EuroMeeting; Rome, Italy, March 2003.

Rare Disease Research and the FDA Orphan Drug Program; The National Disease Research Interchange (NDRI) Genetics of Rare Disease Conference; Washington, DC, March 2003.

Marketing Exclusivity and Orphan Drugs; Food & Drug Law Institute (FDLI) 46<sup>th</sup> Annual Educational Conference; Washington, DC, April 2003.

Orphan Products Development; Regulatory Affairs Professional Society (RAPS) Orphan Products Audio Conference; April 2003.

The Orphan Drug Act: Twenty Years Old and Growing; National Organization of Rare Disorders (NORD) 20<sup>th</sup> Anniversary Celebration; Washington, DC, May 2003.

Orphan Drug Designation and Development in the USA; 3<sup>rd</sup> Annual Swedish International Alfred Nobel Meeting; Karlskoga, Sweden, May 2003.

How Orphan Drug Legislation in the U.S. and the EU Serves Patients With Rare Diseases; University of Salerno, Salerno, Italy, May 2003.

FDA Policies and Procedures: Orphan Drug Approvals; Weaver Symposium on Orphan Drugs and Rare Disease; University of Minnesota, Minneapolis, Minnesota, June 2003.

The Orphan Products Development Program of the Food and Drug Administration; Medicis Pharmaceutical Corp; Scottsdale, Arizona, June 2003.

Developing Treatments for Inborn Errors: Incentives Available to the Clinician; New Developments in Urea Cycle Disorders; Sydney, Australia, September 2003.

U.S. Orphan Drug Development; Therapeutic Goods Administration (TGA); Canberra, Australia, September 2003.

Developing Drugs for Rare/Orphan Disease: Italy; Perugia University, September 2003.

Studying Clinical Trials for Orphan Drugs: The U.S. Experience; Fourth European Platform for Patients' Organizations, Science and Industry (EPPOSI) Workshop on Partnering for Rare Disease Therapy Development ; The Hague, Netherlands, November 2003.

Understanding How Same vs. Different is Determined for Market Exclusivity; The Center for Business Intelligence (CBI) conference on Commercialization of Orphan Drugs, Arlington, Virginia, January 2004

The Scope and Impact of the U.S. Orphan Drug Act; 2004 Regulatory Industry Outreach Conference; San Juan, Puerto Rico, March 2004.

Developing Treatments for Inborn Errors: Incentives Available to the Clinician; 2004 Meeting of the Society of Inherited Metabolic Disorders (SIMD); Orlando, Florida, March 2004.

Orphan Drug Designation and Development in the U.S.A.; the 14<sup>th</sup> Course on Medical Genetics; Gargano, Italy, June 2004.

The FDA's Role in the Investigation and Approval of Products to Treat Rare Diseases; Aplastic Anemia & MDS International Foundation Patient Conference; Baltimore, Maryland, July 2004.

Roadmaps to Resources; Genetic Alliance 2004 Annual Conference; Arlington, Virginia, July 2004.

Opportunities for FDA Support; 23<sup>rd</sup> Annual Leukodystrophy International Conference, De Kalb, IL, July 2004.

You Can Work With the FDA; Presentation at Allergan, Inc; Irvine, California, August 2004.

Overview of the Office of Orphan Products Development; Interdisciplinary Meeting: Office of Rare Diseases, National Institutes of Health, Bethesda, MD, August 2004.

Regulatory Aspects of Epidemiology in Orphan Product Development; Pharmacoepidemiology Adds to Orphan Drug Development Workshop, Bordeaux, France, August 2004.

Developing Orphan Drugs in the U.S.A.; Royal College of Physicians Conference on Managing Rare Diseases, London, England, October 2004.

Orphan Drugs: Actuality & Perspectives for Rare Diseases; Conference with Forum Associazioni rosane Malattie Rare, Pisa, Italy, October 2004.

The FDA Orphan Products Development Program; the First International Symposium on Translational Research for Inherited & Orphan Retinal Diseases; Washington, D.C., November 2004.

The Office of Orphan Products Development of the Food and Drug Administration; the 2<sup>nd</sup> Annual Digestive Disease National Coalition (DDNC) Regulatory Breakfast, Washington, D.C., November 2004.

The FDA Office of Orphan Products Development; Mannkind Corporation, Valencia, CA, January 2005.

The Office of Orphan Products Development of the Food and Drug Administration; International Conference on Rare Diseases and Orphan Drugs, Stockholm, Sweden, February 2005.

Regulatory Issues Related to Orphan Designation and Drug Evaluation for Rare Diseases; Meeting of the Society of Investigative Dermatology, St. Louis, MO, May 2005.

A Global Perspective on Orphan Drug Activity; NORD Corporate Council Meeting, Washington, D.C., May 2005.

Expediting New Drugs to Patients: An Inside Look at the FDA Approval Process; 2005 Hereditary AngioEdema Association (HAE) Conference, Chicago, IL, April 2005.

Orphan Drug Designation and Pharmacogenomics: Options and Opportunities; Cambridge Healthtech Institute Targeted Therapeutics Summit, Washington DC, June 2005.

**Multiple Radio, Television, and World Wide Web Interviews on Subjects of Current Interest, including:**

ABC Nightline; Baldness Remedies, June 1983.

WDVM TV Evening News; Pacemaker Segment, April 1984.

CNN Dollars and Sense; Home Test Kits, June 1985.

American Hospital Association Teleconference; Hidden Risks in Reuse of Disposable Devices, July 1985.

ABC Evening News; Home Test Kits, July 1986.

Channel 5 Panorama Interview; Home Test Kits, June 1986.

WPFW Radio Interview; Health Fraud, July 1986.

National Public Radio; Issue of Orphan Drug Exclusivity, November 1988.

KTC TV, Channel 7, Minneapolis, MN; Health Talk and You Panel Discussion, Chronic Fatigue Syndrome, October 1990.

Tokyo Today Radio; U.S. Orphan Drug Experience, December 1991.

Radio Health Journal Interview with Reed Pence: WMZQ, WGAY, WRC April 1994.

WLIW TV, Channel 21; "Living on the Edge:" June 1994.

ARare Diseases--Today≅ Press Conference: Milan, Italy; April 2000.

IDEA TELEVISION; Washington, D.C.; Cutting Edge Research in Medicine Today, 1997.

Numerous additional Radio and T.V. interviews concerning contemporary health issues.