History

of the

U.S. Food and Drug Administration

Interviewee:	**Stuart L. Nightingale, M.D.**
Interviewer:	**Suzanne W. Junod, Ph.D.** **Robert Tucker**
Date:	**April 7, 2009**
Place:	**Rockville, MD**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

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Interview with Stuart L. Nightingale

April 7, 2009

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RT: This is another in the series of FDA oral history interviews. Today we're interviewing Dr. Stuart Nightingale. The date is the 7th of April, 2009. The interview is being conducted by Dr. Suzanne Junod and Robert Tucker of the FDA History Office. The interview is being conducted at Rockville, Maryland.

Doctor, as I understand, when you retired, you were Associate Commissioner for Health Affairs. We'd like to go back to the beginning of your career and start with coverage of your personal and educational background.

SLN: Okay.

I was born in New York City and raised there. I became interested in medicine because of my stepfather, who was a civil servant in New York City. He was the Chief Medical Examiner for the City of New York for almost twenty years. He was a forensic pathologist.

I went to college at Yale and to medical school at the New York University School of Medicine, Bellevue Hospital. My internship was in medicine and surgery and my residency was in internal medicine. My internship and residency were at Montefiore Hospital and Medical Center in the Bronx, New York. I took a year of anatomical pathology at Bellevue during my residency period, and then I finished my training as a

Fellow in Adolescent Medicine at Montefiore Hospital and Medical Center. It was there that I first became interested in drug abuse because so many of the adolescents were injecting heroin and getting medical complications. The direct effects of narcotics use and the medical complications of drug abuse were fascinating medical problems that for the most part were preventable.

When I finished my training, I was interested in community medicine, so I took a position at the Brooklyn-Cumberland Medical Center and the State University of New York (Downstate) Medical Center, where I was an Instructor in the Department of Medicine and taught physical diagnosis to medical students at Downstate, and taught interns and residents at the Brooklyn-Cumberland Medical Center. I also worked in drug abuse. I set up a narcotic detoxification clinic for the Fort Greene community.

One of the attractive things about the position was that, at the same time, I served as the Medical Director of the Cumberland Hospital Methadone Maintenance Treatment Program, which was part of the innovative methadone treatment approach to narcotics addiction, and that fit right in with my earlier work with adolescents and Community Medicine. This actually was an experimental use of an approved drug, methadone. Methadone maintenance was being developed by Doctors Vincent Dole and Marie Nyswander at the Rockefeller University in New York as a treatment for narcotic addiction, and this was an opportunity to work directly with Dr. Nyswander, who was in charge of the operations of the city-wide network of methadone clinics run by Beth Israel Hospital in New York City. I really enjoyed that work, and it was quite interesting.

RT: Had you taken, in your medical curriculum, any psychiatric training?

SLN: Well, I had psychiatric training as part of my medical training. My primary specialty training was in Internal Medicine, but with treating ill adolescents there was a heavy overlay of psychiatric issues. So I had plenty of interaction with psychiatrists at Montefiore. The Methadone Maintenance Program really was a medical approach to drug addiction, so you were actually providing narcotic replacement and blocking therapy under medical supervision, with counseling by trained ex-addicts. Using methadone in this way was viewed by its proponents like giving insulin to diabetics. Narcotic addiction was viewed as a metabolic disease. The overall network of programs was administered by the Psychiatry Department of Beth Israel Hospital. But it was not a psychiatric program per se, and psychiatry was not an integral part of the program. Consultant psychiatrists were always on call.

RT: So, methadone was a substitute for narcotics.

SLN: Yes, for heroin and other opioid drugs.

RT: Less addictive?

SLN: Well, it was not less addictive per se, but it's given in a way that you are creating a permanent stable dependence, but because of the tolerance the person can function perfectly well, and if the person takes heroin they will not get high. So, in a properly managed program, you don't have the highs and the lows of the street addict, you don't

have dose escalation, withdrawal, or overdoses. Methadone is given out at a specialized clinic. But that's part of the story. At that time, it was a research program so FDA was overseeing it under an IND. I wasn't directly involved in the research component. The research was essentially for the unlabeled use of an approved drug. Methadone was already in use for the therapy of moderate to severe pain, while the unlabeled use was for maintenance therapy in narcotic addiction. This approach brought together issues that were public health and legal (long term administration of narcotics under the strict jurisdiction of the BNDD (Bureau of Narcotics and Dangerous Drugs). There were myriad other legal, regulatory, social, and law enforcement that had to be addressed in establishing these programs It was a novel and important component of Community Medicine at that point, which was becoming increasingly popular at that time, the late 1960s and early 1970s.

And then, after a year or so, my wife and I decided to move to Baltimore, to both work at the Johns Hopkins University School of Medicine. At Johns Hopkins, I worked in Community Medicine, as the Medical Director of the Johns Hopkins Hospital Drug Abuse Center, and was concurrently Research Program Manager for a project developing a model clinic for the elderly in a housing project in East Baltimore, and in teaching in the Department of Internal Medicine and the Johns Hopkins University School of Public Health. I also was an Attending Physician at what was then known as Baltimore City Hospital in East Baltimore, a teaching hospital staffed by Johns Hopkins.

While I was engaged in these activities, I was offered a position in the State of Maryland Drug Abuse Administration as Medical Director. I thought that was an exciting opportunity to go from what I was doing in the clinic to a full-time

administrative program where I was responsible for the medical and regulatory aspects of drug-abuse programs for the entire State of Maryland. This entailed traveling around the State to see extant programs, drawing up regulations for the treatment of addicted prisoners, getting out in the community and having a dialogue with people who thought that using methadone maintenance was "genocidal" because they, mostly proponents of "drug free" therapeutic communities and anti-government activists, claimed it was merely drugging people, mostly minorities, by placing them on a potent narcotic, for life. Through such experiences and debates I developed an understanding of how to function effectively in situations where it was never possible to please everyone. I just kept doing what I firmly believed was right. There were plenty of people who were out to attack me, not me personally, but the program that I was in charge of. There was a lot of that. The local press and TV covered much of this extensively.

A serious and unfortunate aspect of the nascent and growing, but poorly regulated, methadone maintenance approach occurred while I was working at the Maryland Drug Abuse Administration. Because methadone maintenance programs were not fully regulated by the government yet, some individual practitioners were using so-called methadone maintenance treatment to make a lot of money, essentially selling methadone to addicts. These physicians were actually no more than street "pushers." A very large Washington private practice, I won't say program, with a large number of patients who were seeing a particular doctor in Washington to buy methadone, was suddenly closed down by the government, the DEA (Drug Enforcement Administration) predecessor, the Bureau of Narcotics and Dangerous Drugs (BNDD). Since the patients were then already addicted and dependent on narcotics, including methadone, unless they

received a narcotic such as methadone they would go into narcotic withdrawal. So we actually set up an emergency methadone treatment program to take people on an emergency basis and put them on maintenance while working to transfer them to a full-fledged methadone treatment program. This was a successful public health approach to a crisis situation. We published the results of this "holding program" in the *American Journal of Public Health* and presented our findings at the annual meeting of the American Public Health Association.

Because I worked for the State of Maryland Drug Abuse Administration, I was invited to participate in a White House meeting of drug abuse program officials from Maryland, Virginia, and the District of Columbia. The meeting was hosted by a new Office in the Executive Office of the President -- the Special Action Office for Drug Abuse Prevention (SAODAP), whose job it was under President Nixon, to expand drug-abuse treatment, and make it more available nationwide. So the head of that Office asked the regional state-level senior drug-treatment professionals from the Washington area Council of Governments, to come to a meeting. I represented the State of Maryland Drug Abuse Administration at that meeting. It was quite exciting to be invited to the White House to talk about drug abuse treatment, what we were doing in Maryland, and my r previous experience working in methadone programs in New York and Baltimore. Using methadone was becoming an important therapy under President Nixon to make treatment widely available nationwide. Although I was representing the Maryland Drug Abuse Administration at that meeting, it gave me an opportunity to discuss my experiences at the program level in New York and at Johns Hopkins. They were very interested in my

work with Drs. Dole and Nyswander in New York-- the pioneers in methadone maintenance.

Soon afterwards, I was offered a position at the Special Action Office for Drug Abuse Prevention. I saw it as a way to make a real difference nationally in public health and community medicine. I knew that my experience at the clinic, program, and state levels would stand me in good stead as I worked on treatment and rehabilitation policy at the federal government level. So I thought it was a great opportunity, and I accepted the offer to become the Chief, Treatment and Rehabilitation at SAODAP.

I commuted from Baltimore for a year or so, and then I brought my family to Washington. My experience at SAODAP was most satisfying and I felt I was able to contribute a great deal. Further, I really enjoyed the opportunity to travel across the country to conferences and workshops to explain the new and growing methadone program procedures and requirements, to work with the FDA on writing the first regulations for the use of methadone in treatment, and to draft manuals and other educational and training documents. Early on, methadone remained under an IND and was already tightly regulated by BNDD, so there were many complexities to discuss. The issue for us was how to best explain all of this and train people to operate programs as quickly as possible. It was quite challenging and interesting.

SAODAP was a White House-level commission that was set up by legislation to last three years. It was already a year and a half into its work when I joined. I was appointed Chief, Treatment and Rehabilitation, under the supervision of Dr. Peter Bourne who was about to join SAODAP from Georgia where he was then-Governor Jimmy

Carter's chief drug abuse advisor and responsible for Georgia's methadone programs. This was an exciting opportunity.

Among other things, Dr. Bourne asked me to chair two new interagency committees that he was establishing at SAODAP.

One was the Interagency Methadone Treatment Policy Review Board (MTPRB), which was to get together all the Federal agencies across the government that were involved in operating, regulating, and/or funding methadone programs in order to establish uniform policies, regulations, and to overcome any barriers that might exist. This involved working with law enforcement, the BNDD, and the treatment agencies FDA, the National Institute of Mental Health (NIMH), the Veterans Administration (VA), Bureau of Prisons, the Department of Defense (DOD), and others. This was the time that heroin abuse had escalated to become a major problem among U.S. soldiers in Vietnam and a tremendous number of addicted veterans were coming back to the US. SAODAP was in charge of orchestrating a government-wide methadone program and this committee was the staff-level group that was to make it work. Chairing that group taught me a lot about how to coordinate across the government, and it was both challenging and interesting.

The other committee I was asked to Chair was an interagency group to look at drug control issues, the Interagency Committee on Drug Control (ICDC). It reviewed all aspects of psychoactive and narcotic drug use and abuse with both licit and illicit drugs. It concentrated on drug scheduling and quota issues and the effect of drug scheduling on medical practice and drug treatment programs and research on narcotic and psychoactive drugs.

SAODAP was supposed to wind down in another year or so, but at that time an entirely new organization within the Department of Health, Education and Welfare (HEW) was established. ADAMHA, the Alcohol, Drug Abuse and Mental Health Administration, was created. It split NIMH into various components. The drug-abuse components were taken out of NIMH and placed into a separate new agency called NIDA, the National Institute on Drug Abuse. Alcohol components were removed from NIMH and placed into the new NIAAA, the National Institute for Alcohol and Alcohol Abuse. That was the first dedicated agency within the Federal bureaucracy that was dedicated to the prevention, treatment, and research aspects of drug abuse, and a number of people who worked in the Special Action Office for Drug Abuse Prevention in the White House were asked to assume positions at this new HEW agency, NIDA. I was selected to become the Director, Division of Resource Development, at NIDA. In this position, I oversaw a demonstration grants program, prevention and education, and training, and many of the things I'd been involved with before, including domestic and international drug scheduling. I continued to chair the two interagency committees that I had chaired while at the SAODAP. This essentially moved these interagency committees into the permanent bureaucracy -- a major advance.

SJ: Were you primarily dealing with addictive drugs as opposed to things like LSD or marijuana or . . .

SLN: It was all drugs of abuse, both illicit and legitimate drugs, everything.

SJ: Everything. Okay.

SLN: Yes. I was more involved in methadone activities and alternatives to methadone that were under development. Part of the White House program had been trying to facilitate the development of new drugs that might be used for therapy, for example, a long-acting methadone.

Extracting parts of NIMH to create NIDA caused a great deal of consternation among the long-term NIMH staff that were moved into NIDA at senior and mid-levels. They didn't like the concept, but they especially didn't like a lot of people from the White House -- who were quite young and inexperienced in the ways of the bureaucracy -- coming to their turf and telling them how to run things or to be in charge of them. There was quite a bit of friction there. I learned a lot from this.

Anyway, I enjoyed that work, but after a while I didn't like devoting myself only to drug-abuse issues because I'd gotten, I wouldn't say "burned out," but I wanted some new challenges. It was interesting, but not really how I wanted to spend my time in the future. And also, I really didn't like administering grants programs. I was much more interested in regulatory issues, standard setting, practice-of-medicine issues, things that were really more related to my general medical background. And this may be where not having a psychiatric background or a particular interest in psychiatry became part of my motivation to move on. My colleagues at NIDA came mostly from NIMH and were much more psychiatrically oriented.

I looked around and thought to myself that I really enjoy working for the government. My family had moved to Washington. I wondered which agency would be

the best match for my interests. I thought back about the interagency committees that I had chaired and decided that FDA was far and away the most interesting and the most medically-oriented agency, and the one that had people in it that I most respected in my interagency work.

And I'll tell you the three people who stood out, Dr. John Jennings, Dr. Mark Novitch, and Mr. Mervin Shumate, all of whom I'd come in contact with a lot, both at the SAODAP and then, less so, when I was at NIDA. So I went to speak to both Mark Novitch and John Jennings about a possible position at FDA, one I could transfer to from NIDA. It didn't look like they had a specific position available that would be suitable, but they said I should talk to Dr. Richard Crout, who was then the Director of the Bureau of Drugs. I arranged for an interview with him, and I was very impressed with him. He asked me to become one of his Special Assistants, and I could tell from our discussion that he welcomed new people, people who came from outside FDA, but had worked in other agencies. He thought that it was important for FDA to have an infusion of people who had, through previous experience, a fresh perspective, and could add strengths to the overall staff capability. He thought that my background and experience would be a good fit for his next Special Assistant. I was to replace Bob Temple, who was his current Special Assistant. Dr. Crout always had concurrently both a medical Special Assistant and an administrative Special Assistant. When I first took the position the latter was James Belson, and later Jim Morrison was appointed to the administrative assistant position.

I was happy to accept the position at FDA and very pleased to be part of the FDA team.. I would say that some of the people involved in FDA's drug-abuse activities

probably were somewhat concerned to see a person in the Office of the Director of the Bureau of Drugs getting directly involved in some of the detailed issues, especially because I had a strong background in FDA activities through SAODAP and NIDA. But I worked closely and collegially with the people who were writing the FDA's methadone regulations, the Division of Neuropsychopharmocologic Drugs Director, Dr. Elmer (Al) Gardner, and Dr. Ed Tocus, the Chief of the Drug Abuse staff in the Bureau of Drugs at that time.

Working on the methadone regulations and on a wide variety of IND and new drug issues was interesting and challenging. I really enjoyed being there, and I learned a lot from Dr. Crout about all aspects of and responsibilities of the Bureau of Drugs. I did that for about four years, when I was selected by Dr. Mark Novitch, who was recently appointed to head the new Office of Health Affairs (OHA) -- the first Associate Commissioner for Health Affairs -- to become his Medical Deputy. As Deputy Associate Commissioner for Health Affairs (Medicine) my primary responsibility was to serve as liaison to health professional and scientific organizations. Then, not long afterwards, Mark Novitch was asked to become the FDA Deputy Commissioner, by Commissioner Jere Goyan. At that time, I was appointed to be the Acting Associate Commissioner for Health Affairs, initially on a rotating basis, but soon the only one.

My official permanent appointment was in 1982, but I was acting from 1979 until 1982, so I really served in the position of Associate Commissioner for Health Affairs for almost 20 years, counting both the acting and the permanent positions.

And the Office of Health Affairs was an excellent creation administratively. It really combined a lot of things that were interesting to me and were important to FDA.

Although there was no Chief Medical Officer position at that time, the Associate Commissioner for Health Affairs played that role. OHA was the agency's overall medical organization, and I did many things that the Chief Medical Officer would do. OHA, of course, had responsibility for serving as liaison to health professional and scientific organizations, but also as liaison to the human subject protection community, for education and training. OHA had a nascent international staff that needed to be developed and expanded to represent FDA properly internationally.

OHA also had a quasi-judicial role. I was the Hearing Officer for clinical investigator disqualification procedures. This meant listening to the relevant Center present the case against an investigator for violating FDA IND regulations. The FDA Center with its lawyer from the Office of the General Counsel was the prosecutor for these cases. Then the lawyer for the investigator would present their defense -- why the investigator shouldn't be disqualified. That was an interesting process and a critical one for FDA. OHA would write up the proceedings and make a recommendation to the Commissioner for the final agency disposition.

OHA coordinated the agency's domestic and international drug-abuse activities, including drug-scheduling issues. The latter was always challenging and interesting and kept us in close touch with DEA, NIDA, and SAMHSA. I continued to chair the Methadone Treatment Policy Review Board (MTPRB) and the Interagency Committee on Drug Control (ICDC), the committees that had begun in and I had chaired both at SAODAP and at NIDA. These continued to be extremely useful interagency coordination mechanisms. (The Chairmanship of the ICDC began to rotate among the member agencies.) The Methadone Policy Board discussed and drafted policies and regulations

from the ground up. Having the input of the other agencies that would be involved in implementing the policies and regulations was quite salutary even though they were draft FDA regulations. The views of the other agencies were invaluable and their early buy-in was essential. It kept us working closely with our colleagues in other agencies and avoided some potential later disputes. This interagency coordination activity was really important, and as mentioned, something that I had a lot of experience with in my earlier positions in the government -- especially at the White House.

RT: Were you involved in any Congressional hearings during that time for some of the new legislation?

SLN: Yes. I testified at a number of Congressional hearings. I should add that I did serve as one of the three FDA liaison members of the Commission on the Federal Drug Approval Process in 1980-1981. The recommendations, I believe, were influential in helping shape later FDA legislation and policies.

I testified on a variety of issues at the state and Federal level: international and domestic drug scheduling issues, the regulation of methadone maintenance programs, health fraud and quackery, aging, and scientific integrity and misconduct among clinical investigators, among others. These included Congressional hearings in Washington and Congressional field hearings in New York City and Rapid City, South Dakota.

I didn't mention this earlier, but I did a great deal of testifying in the late 1970s at State legislatures, mostly on Laetrile, but some testimony on state programs to legalize the provision of medical marijuana, marijuana to be used for treatment purposes in that

state. I co-authored an article for a legal-medical journal in 1978 with Frank Arnold, in the Office of Federal-State Relations in ORA, on how Laetrile laws affect physicians. It provides an interesting snapshot of what was happening then at the state level with state drug-specific legislation. (See Appendix.)

I was very involved in Laetrile issues when I worked in the Bureau of Drugs. Laetrile, a concoction of apricot pits that contained cyanide, was promoted as a cancer cure. It was a major regulatory and public concern, as was quackery in general. FDA's role was critical in this area. I should note that I was involved in medical quackery issues throughout my career at FDA, meeting many times with historian James Harvey Young and Wally Janssen, providing information to them. I made sure that we kept the health professional community apprised of many quack products and promotions over the years. I was impressed with and worked closely with Paul Sage on Laetrile and quackery in the late 1970s and learned a great deal from him. He was a fierce defender of FDA and public health, and his untimely death was a great loss to the agency.

I testified many times in state legislatures on Laetrile when I was in the Bureau of Drugs. We had a Bureau of Drugs-led task force, a team that Dr. Crout asked me to lead and coordinate. We reviewed the many requests and decided which medical officer should appear before which state legislature. We were always careful to make sure that we were there as a resource to the requesting committee or state health department, not as lobbyists. FDA received many state-level requests, some from legislatures and others from state health departments. We developed model state-level testimony on Laetrile that we all used, updating it as necessary. We coordinated closely with ORA on these requests and in appearances at the legislatures. ORA was our point of contact for this.

Our goal was to try to get the legislatures not to adopt legislation which they had understood would allow Laetrile to be used legally in those states. We made it clear that regardless of what was written, there was a Federal hook or nexus that could be invoked by FDA, some element of interstate commerce, even if it was the glass in the bottles. Even if they were to adopt legislation, FDA would prohibit its use. Our main arguments, however, were scientific: a lack of any demonstrated safety and efficacy, and the fact that it was a deadly poison.

SJ: And were you ultimately successful?

SLN: Yes, we were. Again, it was one of those issues where there were many people against its use and many people for its use. There were fights. Nobel laureates weighed in on the Laetrile side, several, unbelievably, as Laetrile proponents. A lot of really fanatic people and entrepreneurs were harming desperate cancer patients and making a good deal of money at the same time. One of the final blows to Laetrile, as I recall, was a study conducted by NCI.

I testified in the Massachusetts state legislature in Boston, where parents had given their baby a lethal dose of Laetrile. There were many deaths caused by Laetrile. It was an international issue as well.

But, getting back to the hearings, I did testify at a number of Congressional hearings. These included hearings on scientific misconduct in clinical trials, FDA's activities that related to the elderly -- especially health fraud -- hearings on international

and domestic drug scheduling, hearings on patent-term restoration issues, and two field hearings.

I testified at a Congressional field hearing in Rapid City, South Dakota, on Willard's Water, a quack product that was earlier featured on *60 Minutes* for is success in growing mammoth cucumbers, and at a field hearing in the New York City Federal Building on the FDA's regulation of methadone programs.

There were other ways that I was involved in legislation. As Associate Commissioner for Health Affairs, I was involved in reviewing FDA draft testimony, testimony of other agencies and departments on FDA-related legislation, and going to internal FDA meetings where bills were being discussed. All of this was an important activity for OHA, but was not a major activity of mine. Others in OHA were involved in this, as well.

RT: I just thought it might be of interest because of your background in this broad area. I think you did part of the writing in the area of physician and patient information, where physicians would have to fully inform patients and so on. Was that during your tenure with FDA?

SLN: Yes. These are separate topics, in a way. We mostly worked with health professionals to make sure they knew what they needed to know to take care of their patients. We also vigorously worked to assure that information on drugs were directly available to patients through various routes, but especially through patient information leaflets, later Medication Guides.

When I began work in the Bureau of Drugs, I immediately became directly involved with the *FDA Drug Bulletin*, a major communications vehicle for reaching a broad spectrum of physicians, physicians in training and physicians in practice as well as pharmacists, nurses, dentists and other health professionals. I didn't mention it earlier, but my initial interest in FDA came when I was a resident in Internal Medicine. I regularly read the *FDA Drug Bulletin* and found it quite relevant to my work in the hospital. It was an important vehicle that FDA had for getting physicians to report adverse drug reactions. The Adverse Drug Reaction (ADR) form was on the back of the Drug Bulletin itself. It was also quite interesting overall.

I was very interested in the unlabeled use of approved drugs as a medical-practice issue, because, although physicians were allowed to prescribe for unlabeled uses, they were quite concerned about malpractice and liability issues, and about lack of reimbursement for "off label" prescriptions. By the way, the "off-label" term didn't exist in those days. It was then the "unlabeled use of an approved drug." Some were also concerned about what it might mean professionally if they were prescribing off label for drugs on a large scale. This related especially to quackery issues, for example, EDTA therapy. "Chelation therapy" with EDTA was truly quackery and hazardous. Promoting and dispensing approved medical products for unapproved indications on a large scale in specialized clinics was a serious problem that FDA confronted with legal actions. We worked closely with the GC and ORA on dealing with these issues.

The FDA *Drug Bulletin* was the vehicle in those days to reach health professionals. We wrote an important and influential article in the *Drug Bulletin* around 1982 on the unlabeled use of prescription drugs that physicians found especially helpful.

I was the FDA's liaison to the American Medical Association, and I began going to their biannual House of Delegates meetings in 1984, at the invitation of the AMA as part of the United States Public Health Service (USPHS) delegation

The initial invitation was because the AMA was particularly interested in hearing directly from FDA on patient package inserts (PPIs) and direct-to-consumer advertising -- medical practice and pharmaceutical manufacturer issues wrapped together. Usually, these delegations were headed by the Surgeon General. Some of the most memorable meetings were those when Dr. Koop lead the delegation and actively participated in all facets of the meetings. I made presentations at the Science and the Public Health References Committees at the AMA House of Delegates on proposed resolutions and AMA reports that related to FDA. These included scientific, medical practice, public health, and health policy issues. It was an important opportunity to reach this influential group composed mostly of practitioners in order to help them understand what FDA's views were on the multiple proposals for consideration at the House of Delegates. So this was important, even beyond whether a particular resolution or report was adopted. My participation on the USPHS delegation began when the AMA requested an FDA representative to come to the House of Delegates meeting in Chicago and explain FDA's views on Direct-to-Consumer Advertising and Patient Package Inserts. Participating in these AMA meetings became an integral part of the Office of Health Affairs' activities, and this greatly facilitated my role as liaison to the AMA on all medical practice issues, including many unrelated to the House of Delegates meetings. Later on I was accompanied to many of these House of Delegates meetings by Dr. Peter Rheinstein,

Director of our OHA Medicine Staff. This was especially helpful when we had many FDA issues being addressed concurrently in two different Reference Committees.

The most important and visible opportunity to reach practicing physicians came when the Editor of the *Journal of the American Medical Association, JAMA*, Dr. George Lundberg, offered FDA a monthly column in *JAMA*. It was to be a dedicated one-page "column" in which Dr. Lundberg wanted us to highlight the most important FDA issues and topics that would be of interest and value to practicing physicians. In my role as Associate Commissioner for Health Affairs, Dr. Frank Young asked me to be the editor of that column. This meant that I had the responsibility for selecting the most important current FDA issues that I thought practitioners needed to know about. We would be able to pick 3-4 separate topics per monthly column that could be addressed succinctly in a brief paragraph. We looked for what was hot; approvals of important new drugs, orphan drugs, treatment INDs, etc. The time from submission to *JAMA* to actual publication was only about six weeks, an exceedingly brief time for having anything published in a major medical journal with worldwide readership, in those days. Many of the columns were published in *JAMA*'s foreign language editions. There was no online publishing.

While we were guaranteed independence -- a condition of our agreement to the monthly column -- the *JAMA* editorial staff did propose edits. We mostly accepted these, except when a slight wording change actually changed the meaning. We were able to resist these changes by defending our initial wording as necessary because we were a regulatory agency.

The investigational use of drugs for treatment purposes was an issue I was always interested in and involved in during my FDA career. It became an important topic that

we wrote about in the *JAMA* column. Physicians needed to know about newly designated Treatment INDs to help their patients. I would like to note that I was very fortunate to have Carol Kimbrough, my Special Assistant, working closely with me on the "From the FDA" column, in *JAMA*. She was key in assuring the accuracy of everything that ended up in the column and in coordinating with the JAMA staff to ensure any changes in proof by the JAMA editors were either approved or, rarely, rejected. Carol's experience as a regulations writer in CDER and her training as a lawyer were very valuable in this activity.

We also authored a number of articles for *JAMA* on a variety of important FDA-related medical topics for practitioners. Dr. Frank Young was the Commissioner at that point, and was quite interested in communicating FDA's messages in medical journals. Dr. Young and I and others collaborated on many articles and "Special Communications" in *JAMA* and other publications, including the *WHO Bulletin* and HHS's *Public Health Reports*.

Aside from writing articles and serving on the Editorial Board of the *FDA Drug Bulletin* and the *FDA Bulletin* (the successor to the *Drug Bulletin*) and the *JAMA* "From the FDA" column, speaking to medical and pharmacy groups was an extremely important outreach function for our office. Direct interaction and communication with health professional and scientific organizations was not only critical to getting the word out about what FDA was doing and what FDA wanted them to know, but it was an opportunity to hear about their concerns and problems directly. Informal discussions at these meetings with our stakeholders were critical. And I liked to do that. It was good to

go out and talk to practitioners informally, not just about what they saw as problems but what new issues they thought needed to be addressed by FDA. I would come back from an AMA meeting or from a speech someplace and say, "Here's what we need to be working on. Here's what we need to write about, to clarify this for our stakeholders." So that direct interaction was very important. In fact, OHA hosted quarterly health professional organization meetings. Most were attended by Washington office FDA liaisons but some would come from other cities where the organizations were headquartered. This depended on the agendas that we developed. AMA scientific and technical staff routinely came from Chicago.

We took a similar approach to working with the human subject protection community. We would regularly address the annual meetings of PRIM&R, Public Responsibility in Medicine and Research. We would come back from those meetings with a list of items to deal with or clarify. Dr. Halyna Breslawec and Bonnie Lee were especially helpful in organizing our participation and in interacting with PRIM&R and various other groups, as well as with our counterpart HHS organization for human subject protection – initially the Office of Protection from Research Risks (OPRR) at NIH, and later the successor organization, the Office of Human Research Protections (OHRP) in the Office of the Assistant Secretary for Health. We co-sponsored quite a number of regional meetings on human subject protection topics with OPRR.

RT: Well, I think there was an issue of whether physicians were candid or open enough with patients about the treatments, or were they giving too much or not enough information to patients. Was that something which was considered along the line?

SJ: Related to that, the patient package insert (PPI) was an important issue for FDA. It started with the oral contraceptives and the activism that women's consumer groups took in that area. I know Dr. Goyan was interested in patient package inserts, so it would be valuable to hear anything you have to say on that back-and-forth exchange.

SLN: The patient package insert issue was quite a controversial one, and one that industry was very much against. In addition, there was controversy about the role of pharmacists and what pharmacists should tell patients. Many physicians didn't like to have their patients told about the side effects and official indications for drugs at all, not by pharmacists or in leaflets. Physicians weren't doing it themselves. This was an earlier era where many physicians didn't tell patients much about their diseases. So the whole concept behind the patient package insert program was to give patients some independent factual information. – what they should know about the drug that they were going to start or continue taking. We thought that was very important. And actually, at the end of the Carter Administration, FDA published a final regulation on PPIs, patient package inserts. It was primarily to implement a pilot program, and it was viewed to be an important first step in this overall approach.

When the Administration changed, the new Administration rescinded the patient package insert regulation, on the basis that it was better to actually encourage the transfer of information voluntarily -- to get physicians talking with their patients, pharmacists talking with their customers, and to stimulate patients to ask questions. The idea was to implement a voluntary program without the use of leaflets developed, approved by, or

mandated by the government. So an organization that Congressman Paul Rogers was asked to lead -- the National Council on Patient Information and Education (NCPIE) was formed by FDA, industry, and health professional organizations. I served as the official FDA liaison to that organization for almost 20 years.

NCPIE did everything it could to promote communication among health care professionals and patients, as opposed to having government-developed and mandated information sheets for patients. My personal bias always was that Patient Package Inserts were quite important and should be accurate and universally available, and that the rescinded pilot program to evaluate them would have been quite instructive. We cooperated completely with NCPIE and its members and did everything we could to promote the voluntary approach. I found NCPIE to be very helpful in this whole process. Nonetheless, there was always the feeling that, for certain drugs, you really did need to have government-approved patient drug information made available directly to patients. Several years later, a variety of voluntary patient information and leaflets began to be distributed by chain pharmacies, drugstores, and commercial vendors and other outlets. Although not perfect, it was a good initial approach.

Later, there was legislation that required evaluation of voluntary PPIs. If they were not being developed and used, and were not factually correct, then the government would need to step in and do more. And then in the late ‘90s, the FDA was given the authority to require Medication Guides, based on the official FDA drug labeling for drugs that met certain criteria. That was all to the good.

This contentious issue related to another FDA issue. In permitting direct-to-consumer advertising of prescription drugs, FDA demanded factual brief summary

information so that the reader would be informed of certain basic risks and benefits. The kind of information that should be in a patient packet insert is the kind of information that you'd like to see in drug advertisements in the media.

There were some bizarre historical issues. There was one point when FDA required a scrolling of information for direct-to-consumer advertisements on TV. The ads had tiny type and the scroll moved quickly across the screen. This met the letter of the law, but wasn't worth much in terms of informing the public. But that all changed, and there was a continued evolution in FDA requirements for DTC advertising on TV over the years -- real improvements.

OHA's role was to explain and "translate" the FDA regulatory requirements in areas such as this, to our constituency of healthcare professionals. The AMA was always interested in and concerned about DTC advertising and followed this issue closely. This was not popular with most practicing physicians for a variety of reasons.

RT: You mentioned in passing the pharmacies, pharmacy interest or the drug manufacturers -- I should correct myself -- not liking pharmacists getting out of their bounds in counseling people on therapies.

I was raised in a little one-horse town in South Dakota and our pharmacists, well, we had one physician and one pharmacist, and people would often counsel with the pharmacist on routine things like colds and so on. He was very good, really a community service. In many small communities that was not an unusual situation.

SLN: Each profession had its own role. Industry was against patient package inserts because of its own issues, especially liability and the fear of frightening patients.

Pharmacists actually wanted to counsel and were looking for additional roles to make themselves more useful in terms of serving the community. That wasn't a problem. They embraced handing out voluntary leaflets, and this role certainly served their purpose.

Doctors were concerned about a number of things. This included needlessly scaring patients and also, as with responding to patients' questions about direct-to-consumer advertisements, the need to spend additional time with patients on what they viewed as not critical.

RT: If I remember correctly, when Commissioner James Goddard was heading the agency, he spoke of the corner-drugstore role of drug use counseling. Maybe that was associated with Vice President Hubert Humphrey, too. I think Dr. Goddard recognized that the pharmacists could play an educational role to supplement or complement that of the physician in minor illnesses and minor health problems.

SLN: We all agreed this was important. Dr. Goyan, a pharmacist, promoted this vigorously. We all thought that pharmacists did have an important role to play, physicians had an important role to play, and the industry had an important role to play also. Through the '80s and '90s, NCPIE, and its member organizations, including FDA, promoted communication and voluntary patient information in speeches, presentations, and documents. But one of the concerns voiced by many about the patient package-insert

program, interestingly, in particular from industry, was that it would frighten patients, and they would not take drugs prescribed for them. Well, that's quite humorous now given the fact that when you turn your television set on, you see drugs advertised with the most horrendous side effects and adverse effects, including death, and it doesn't seem to reduce the demand for those drugs. But things have changed tremendously now. Certainly, we all recognize the importance of arming the patients with good, factual information in lay language with at least the most critical information for certain drugs mandated by the government.

SJ: And this was the time period in which the *Physicians' Desk Reference* (PDR) became a popular supplement for laymen.

SLN: That's right.

SJ: Something that had never been envisioned before.

SLN: That's correct. Of course, the fact that FDA labeling, which is essentially what the *Physicians' Desk Reference* contains, was available to the public already, undercut some of the arguments against patient package inserts. So if the people could read the PDR, then why shouldn't they have that information in an abridged document, tailored to the patient, easily available with the drug? We were also aware that in Europe information for patients was contained in the unit-of use packaging that was routinely dispensed to patients by pharmacists.

That was an interesting era, with much contentiousness about patient package inserts and direct-to-consumer advertising. Many of the arguments were tied directly to the economic interests of the profession and the industry.

SJ: Do you remember any particular PPIs that were particularly controversial, or did that not come across your desk particularly often?

SLN: I don't remember a specific contentious drug. Clearly, earlier, PPIs were mandated for oral contraceptives and these were packaged with the product, so-called "unit-of-use" packaging. I do not recall that this was controversial, especially since the pharmacists did not need to be involved in handing out additional leaflets.

Of interest was the fact that we were aware that in Europe information for patients was contained in the widely used unit-of use packaging routinely dispensed to patients by pharmacists. Of course, this was not the way most drugs were dispensed in the US.

The regulation for the rescinded pilot program had had some specific drug classes, as I recall, but the concern was more about the overall issue than the specific drugs that would be selected for the program.

A major anti-PPI argument by industry was that there needed to be a "learned intermediary," the physician, providing this drug-specific information to a patient. Things quieted down with the success of NCPIE and the passage of legislation that mandated reports from FDA evaluating the quantity and quality of voluntary patient information. The latter included a tripwire. If there were not such-and-such a percentage

of factually correct voluntary patient information on prescription drugs, by a particular date, then FDA would have to step in with a mandatory program.

RT: I think you were involved probably with Dr. Young in the AIDS issue, when there were a lot of complaints on the part of folks who had this disease about the lack of empathy about this health problem. The agency had fast-tracked, cleared some possible beneficial drugs. Do you want to speak a little about that?

SLN: Yes. The main issue was getting safe and effective drugs to patients as quickly as possible for the many novel and serious opportunistic infections affecting AIDS patients such as Pneumocystis carinii pneumonia (PCP). Some of these drugs were investigational and used for what were earlier rare outbreaks of infections among laboratory workers. Many required entirely new drugs. Both had to go through the FDA drug-approval process to become widely available.

This is where the treatment IND approach, a new type of IND that was especially well suited to dealing with complications in HIV/AIDS patients, entered the picture. Other new FDA approaches including the accelerated approval regulation for drugs and biologics and the "parallel track" program were implemented. A lot was going on. We published a great deal of information about these new approaches and mechanisms as well as the specific products as they became available in the "From the FDA" columns in *JAMA*.

Additionally, our office was very involved in reaching out to the gay and lesbian physician community to help them treat their patients with the best available therapy,

even if it was then only investigational. In many cases, our outreach was to physician practices and clinics that catered specifically to patients with HIV/AIDS. Since some of this involved using treatment IND drugs, or other drugs that were still under standard IND protocols but available for "compassionate use," it was our job to inform them about FDA requirements to utilize investigational products and, at the same time, collect information that would be useful to FDA, at least in partially supporting marketing approval for the drugs.

I worked closely with Mary Pat Couig, a nurse in our OHA Medicine Staff, on outreach to the gay and lesbian physician community. We met with a number of these groups; the most prominent and the easiest to work with was Physicians for Human Rights, a gay and lesbian physician organization that originated as a local San Francisco group. We spoke at their annual meetings and met with their leadership on many occasions. We arranged meetings that included Dr. Young and relevant Center Directors to talk about what could be done to simplify things and to make drugs and biologics more readily available. We had quite a major coordinating role in that. We also worked closely with NIH HIV/AIDS staff, including the current Director of the new FDA Tobacco Center, "Bopper" Deighton and Jack Killen, who is still at NIH in the Center for Complementary and Alternative Medicine. Together with the NIH, we met with PhRMA (then the PMA) on a number of occasions on HIV/AIDS drug development and access issues. We did a great deal at that point to try to respond to the needs of the HIV/AIDS community.

And, of course, our work with the HIV/AIDS physicians overlapped with our work with the larger medical community. Treatment INDs were very important for other

diseases and conditions -- not just HIV/AIDS -- and the new regulation establishing it and its implementation was an extremely important new FDA approach for all physicians and patients in the mid-‘80s.

RT: Were you involved in this meeting that Commissioner Young had with some of the AIDS activists? You know, we had a demonstration in front of the building at one point. Then Dr. Young, either before or after that, met with the group ACT UP, and I think largely disarmed them from their belligerence by explaining what the agency could and would try to do.

SLN: I was here the day that they blockaded the building. I wasn’t directly involved in speaking with them, and I don’t know precisely what Dr. Young did on that occasion. But I did accompany Dr. Young, Paul Parkman, and other Center directors to Boston to an annual meeting of gay and lesbian HIV/AIDS organizations. I organized our involvement with the FDA Boston District Office.

RT: That’s the one I really had in mind.

SLN: Yes, I went to that meeting. It was an opportunity to explain to this large activist group what FDA was doing about access to drugs and the new procedures FDA had put in place and we were planning to do. Dr. Young had an excellent speech prepared, and it was going very well until at one point suddenly there was what was known as a “die-in,” where all the people in the audience dropped to the floor and lay down. It was a routine

form of protest by AIDS activists at that time. There was no way of continuing with presentations or dialogue during this disruption. It was a major demonstration, and we left abruptly at that point, before the planned presentations were finished. We left immediately through the kitchen, led out by Mary Pat Couig, who was then an inspector in the Boston District Office and assigned to assist the Commissioner for this meeting. She had wisely scouted out an escape route earlier if any violence erupted. You may recall that during this period Dr. Young had numerous death threats.

In spite of our abrupt departure, going to this meeting in the first place was the right thing to do. Having the FDA Commissioner and his senior FDA leadership team come to Boston to engage with this group was an important statement. This was in addition to the Commissioner and senior staff speaking with HIV/AIDS advocacy groups and meeting with their leadership in small sessions and larger meetings over a number of years was critical. As I mentioned earlier, I believe our substantial work with this community was quite helpful to them and to us, especially in informing us of the needs at the practicing physician and patient levels. ACT UP was very involved in all of this. Its modus operandi was to keep engaging with us and complaining loudly about what they saw as delays and outmoded approaches, and failure to get drugs out. Making investigational drugs available for treatment use as soon as possible and accelerating the drug approval process were key. So FDA was very responsive. We did reach out, we did work with our sister agencies such as NIH on this, and with the pharmaceutical industry, and we were able to make unique contributions that only FDA could make.

We went to small meetings and large meetings in Washington and New York. We went around the country meeting with HIV/AIDS doctors in New York and San

Francisco, informing them about how to comply with FDA requirements while using investigational drugs that would be useful for HIV/AIDS and infectious complications. The latter, at that point, as I mentioned, was the key concern. FDA's appearance and presentations were welcomed at these meetings. In fact, when the Sunday New York Times covered a major meeting on HIV/AIDS in New York, it was the photo of the FDA panel that was on front page.

I should mention that Mary Pat Couig in our Medicine Staff and I worked closely with the FDA San Francisco District Director, Mark Roh, who did a terrific job in facilitating our meetings with health professional organizations, AIDS activists, and community physicians specializing in the treatment of HIV/AIDS patients.

RT: I assume it involved cooperation on the part of the professional physicians that were in that kind of treatment?

SLN: Yes.. They were extremely pleased to have FDA help them understand the regulatory and practical issues.

We even developed, in our office, a handbook explaining what a community practitioner should know about investigational drug use. The handbook was a compilation of all the relevant FDA regulations and policies along with explanations in language tailored to the needs of practitioners. This was especially useful for those who wanted to use Treatment IND drugs for individual patients. Mary Pat Couig was key to our development of the Handbook.

A few years later, at least one company actually did prepare a similar compilation for their investigators, including community practitioners. These pulled together IND and human subject protection regulations. We were pleased to have taken the lead in developing the model.

SJ: Was Bonnie Lee involved at this point?

SLN: No. I do not recall her being substantially involved in the HIV/AIDS community physician educational outreach program. Our Medicine Staff was the lead OHA component in this. I'm sure she was involved in reviewing the written materials and remained involved in the more general ongoing routine IRB education and training initiatives through her work in the Health Assessment Policy Staff in OHA-- informed consent, and IRB regulatory activities, and our work with PRIM&R.

Bonnie Lee was instrumental in the development of the OHA Information Sheets, a series of non-regulatory, plain-language brief informational documents that OHA initiated in the late '80s, early '90s, that were designed to help clinical investigators, sponsors, Contract Research Organizations (CROs), and IRBs comply with FDA's human subject protection requirements. They included documents on Treatment INDs and Central IRBs, as well as on the more traditional human subject protection issues such as informed consent and continuing review. These too were meant to assist the HIV/AIDS physician community.

To sum up, we tackled the HIV/AIDS issues head-on with the physician community that specialized in treating HIV/AIDS patients. Dr. Young was always

enthusiastic and responsive, as were the Center directors. We really did everything we could to be responsive, including developing the new regulatory vehicles that would make drugs and biologics available as quickly as possible for therapeutic use. I mentioned the accelerated-approval process, the Parallel Track program, as well as the treatment IND as examples. And there were many things we did in addition to be responsive. We made full use of the "From the FDA" column in *JAMA* and the *FDA Bulletin* to explain and promote these special programs and new mechanisms. The agency was highly mobilized to deal with this.

RT: What were some of the other major issues that you dealt with in the agency in the several administrative capacities you had?

SJ: At the time I came to FDA, you had a large staff. So, can you talk a little bit about the organizational evolution of your office?

SLN: Yes. OHA had a relatively large staff, and was responsible for a wide variety of domestic and international programs. Its actual size varied over time but at its peak OHA had 50 or so staff members and rotating detailees and fellows.

The Office of Health Affairs was established in the late '70s with Dr. Mark Novitch in charge as the Associate Commissioner. I don't remember what the precise initial number of people in the office was, but my guess is maybe 25 or so. It had three major components. There was an Office of Medicine, an Office of Science, and a smaller International Affairs Staff that reported directly to the Associate Commissioner. The

other two offices were headed by Deputy Associate Commissioners. My initial position in the Office was Deputy Associate Commissioner for Health Affairs (Medicine). In 1982, there was a reorganization which resulted in an Associate Commissioner, me, at the SES level and one overall Deputy, Allen Duncan, at the GS-15 level, heading the Office. There were three staff Offices, each headed by a staff Director at the GS-15 level -- The Medicine Staff (MS). The International Affairs staff (IAS), and a staff office that was responsible for a wide variety of issues, the Health Assessment Policy Staff (HAPS). HAPS covered human subject protection issues, drug scheduling, and other drug-abuse and control issues. HAPS also provided the support for the Clinical Investigator Disqualification hearings, writing both the record of the hearings and the document proposing disqualification or restrictions or no action that was then sent to the Commissioner for the final determination and action. HAPS was often the locus in FDA for issues where there was no other obvious or appropriate place in the agency to handle them. In fact, OHA took on a variety of novel issues over the years that needed to be handled by FDA. The HAPS Staff included people with a variety of expertise and was able to handle unusual kinds of things, especially new ones that cut across the agency and thus needed to be handled at the Office of Commissioner level. Examples included dealing with such issues as biodefense, tissue banks, and xenotransplantation.

When OHA was created, it was the first time there was a locus for international activities outside of the Office of Regulatory Affairs (ORA). While ORA had an important regulatory role internationally, at Headquarters it had only one or two people, whose duties were primarily to host visits by foreign regulatory officials, to show them around and explain FDA functions. Establishing an agency-wide programmatic locus for

international affairs that could be proactive in dealing with the international community was truly one of the major contributions of the Office of Health Affairs. It was quite exciting, and something that Mark Novitch felt strongly about. It grew over the years from a small staff to a major FDA program and did a great deal to facilitate and promote FDA's work internationally.

There were some specific international programs that FDA had been involved in, mostly at the Bureau level. One example was the Codex Alimentarius Commission, a joint FAO (Food and Agriculture Organization) and WHO (World Health Organization) program that is led in the U.S. by USDA. Another was, and medical devices trade-related activities with Japan and other countries that were carried out under the auspices of the Office of the United States Trade Representative (USTR). Our role, initially, was to promote and facilitate the few extant international programs and help them flourish, where our assistance would be helpful, but not disturb or inhibit them.

In the drug area, there was really no structured international program at all at that time. However, an important international effort spearheaded by the leadership of the Bureau of Drugs had just begun. In fact I was fortunate to have been in on the ground floor, not too long after I left the Bureau of Drugs to go to the Office of the Commissioner. I assisted Dick Crout and Jerry Halperin in planning the first meeting of the "International Conference of Drug Regulatory Authorities" (ICDRA) in Annapolis in October 1980. The U.S. had organized this meeting of like-minded regulators from a number of European countries and some others as well as the WHO pharmaceuticals program to begin to discuss the regular exchange of information and to look at whether there could be a discrete program of international harmonization for regulatory

requirements for pharmaceuticals. The meeting was successful and it was agreed to continue these meetings on a biennial basis.

At the conclusion of the Annapolis ICDRA, while harmonization was considered an important issue for the ICDRA, it was decided that the time was not ripe to deal with international harmonization.

The initial focus for the ICDRA became information exchange. But that low key approach was a critical first step.. It was a major advance to have regulators talking to one another and sharing best practices in review and other important matters, including problem areas that needed attention in an international forum. And, of course, it wasn't just communicating at these biennial international meetings. It led to and facilitated the development of both informal ad hoc contact and more formal bilateral communications and the gradual development of a network of drug regulators administered by WHO that would communicate directly in the interim.

In fact, one of the most important outcomes of the early meetings was the establishment by WHO (World Health Organization) of a contact list of FDA counterpart agencies worldwide with points of contact, distributing it worldwide, and then initiating a global rapid communications information alert system by fax.

The Office of Health Affairs continued to promote the biennial ICDRA meetings held sequentially in different countries around the world -- rotating country to country, with WHO serving as the permanent Secretariat. We worked with Drugs and with Biologics on identifying the most important agenda topics for the meeting and shared our proposed topics with WHO and the host country, and then planned FDA involvement.

OHA participated in all facets of planning and attended the ICDRA meetings. OHA would ensure the most appropriate Center representation from FDA.

I should add that these meetings are still going on; discussing issues of importance to drugs and biologics regulators. WHO continues to co-host the meetings with a different country every two years. OHA did a great deal to help the ICDRA evolve. Much credit should be given not only to Dick Crout and Jerry Halperin but also to the major WHO pharmaceutical focal points, starting with Dr. Vittorio Fattaruso. Drs. John Dunne, Juhana Idanpaan-Heikkila, and finally -- and still -- Lembit Rago all worked hard to make these meetings successful and to keep in touch in the interim on a regular basis with the national regulators. A WHO Drug Bulletin was begun. WHO made sure that the ICDRA was not just composed of the major countries with advanced regulatory authorities that were the original organizers and participants in the first few meetings, but brought in the middle income and developing and resource-poor FDA-counterpart agencies. This was an effective way to provide technical assistance and foster communication and collaboration among all drug regulatory authorities.

Another major international program that owed a great deal to the work and collegiality of the ICDRA, and actually was hatched at an ICDRA meeting, was the ICH (International Conference on Harmonization). The ICH was a true harmonization activity. Its complete name was “The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.” By 1991 the major drug-developing countries’ national regulatory authorities were ready to begin to harmonize among themselves to overcome bureaucratic barriers to drug development. The head of Pharmaceuticals program in the European Commission, Fernand Sauer,

during lunch at the Paris ICDRA, floated the idea. He asked the FDA and Japanese representatives what we would think of having a harmonization program among the major drug-developing countries -- the U.S., Japan, and the European Union, through the European Commission, that, importantly, would include each country's pharmaceutical manufacturers' associations as partners.

The fact that this harmonization effort included industry was critical to its success. We worked with the brand-name industry organizations in each country, as well as with the international pharmaceutical trade association, the IFPMA (International Federation of Pharmaceutical Manufacturers Associations). The IFPMA served as the overall Secretariat.

The ICH was adopted by the three countries/regions along the lines as proposed after much discussion.

We also invited official observers -- WHO and Canada -- initially, and they accepted.

Since its formation in the early '90s the ICH has done a tremendous amount of work in harmonizing guidance documents on safety, efficacy, and quality requirements for drugs and biologics for marketing approval applications. But, as I say, it grew out of some of the earlier harmonization efforts. This was an example of the type of leadership and coordinating role the Office of Health Affairs played. Although we did not participate in the technical discussions, we saw that the right people from the agency were involved in this continually. CDER took the substantive lead initially, but soon CBER was fully engaged. Our job was to make sure that everyone was talking to one another internally, and that we were on target for producing the necessary technical

documents at each stage. The support of the Commissioner's Office was critical to overall progress. In collaboration with the Centers, we organized the major regular biennial conferences that rotated among the three members that hosted the meetings. The leadership of the member countries' drug regulatory authorities and of the industry associations led the delegations to the biennial conferences. They were each accompanied by their technical experts.

In my view the ICH is the premier FDA example of successful international harmonization. According to reports, the ICH continues to be a model for international harmonization for other parties that wish to harmonize. From recent personal experience with the Good Clinical Practice issue, the ICH Guidelines in this area are recognized and widely utilized globally.

I will mention a few other international harmonization-related activities where OHA provided leadership and coordination.

We had become quite involved with the Office of the U.S. Trade Representative (USTR) in a number of initiatives. USTR was the lead U.S. organization that dealt with the GATT (General Agreement on Tariffs and Trade) and, later, its successor, the World Trade Organization (WTO). FDA became a valued member of the U.S. government team that negotiated the transition to the WTO.

While CDRH had been involved as a consultant to USTR for medical devices trade-related issues, CDER really hadn't been involved with USTR earlier. That all changed with the European Union internal harmonization initiative known to us in the

U.S. as "Fortress EC 92." Because of the pharmaceutical trade concerns about this effort within Europe, OHA took the lead to assure that CDER and the other FDA Centers were properly engaged in this USTR-led effort. We began providing more systematic assistance as a resource to USTR, across the board: in Drugs, Biologics, Devices, and Foods. This brought us closer together with sister U.S. government Departments such as USDA and the Department of Commerce. We became especially active in responding to the EU's "precautionary principle," which had major implications for trade involving all of FDA. This also led to greatly expanded and structured FDA communication with and assistance to other U.S. government agencies in FDA trade-related matters. USTR involvement with FDA continued and expanded greatly.

Other issues that we became involved in were the European Commission's rejection of Genetically Modified Organisms (GMOs), an especially important issue tied to the EC's embrace of the "precautionary principle."

This dovetailed also with issues that had been simmering for many years at WHO that related to drug patents and WHO's Essential Drugs Program. The focus here was on the WTO TRIPS agreement (Agreement on Trade Related Aspects of Intellectual Property Rights).

We were deeply involved in the major revisions to WHO's pharmaceuticals program, "the Revised Drug Strategy," that had its origins in an international conference convened by WHO in Nairobi in 1985, in which Commissioner Young and I participated.

Now, I will get back to the organization and growth of OHA. Over the years, it kept growing. The largest number of staff in OHA probably was 50 or so in the 1990's.

Our staff was excellent, Most had earlier experience working in the various FDA Centers and that experience was invaluable to our success.

In my view we managed the staff so that it successfully accomplished its mission. There was a substantial decrease in staff when most of the international program was split off, as I will describe.

I was very fortunate to have Pam Pisner working closely with me from the time I joined OHA until the time the office was disbanded. She held a variety of titles over the years in the Immediate Office of OHA. She was knowledgeable, professional, and well liked by all within and outside of OHA. Ken Flieger a very talented writer/editor with longstanding experience in the Office of the Secretary, was my Special Assistant for many years, and later Carol Kimbrough, a lawyer who had worked in CDER, filled that role exceptionally well. Both were great to work with. Allen Duncan, my Deputy, was a seasoned and capable administrator with broad knowledge of agency programs and administrative procedures and gave OHA the support it needed over many years.

Our goal was to help the Commissioner and the Center Directors carry out their work most effectively. This meant our carrying out targeted outreach to health professional and scientific organizations and to the international community and participating in meetings and serving on and leading delegations in multilateral and bilateral fora. The Center Directors were quite happy to have us helping them. One Center Director made it very clear to me, initially, that our assistance wasn't really needed. That was in the early 1980s. By the late 1980s he was happy to have us working closely with his staff to carry out their mission. Much depended on the personality of

each Center Director. We obviously tried to accommodate his or her wishes, and to be as helpful as possible in the manner they desired.

In addition, until Dr. David Kessler became Commissioner, OHA had the strong support of the Commissioners, Acting Commissioners, and Deputy Commissioners in our programmatic efforts with the Centers and our relations with other Offices in the Office of the Commissioner.

OHA was always involved in many diverse issues. In most cases it was clear that OHA had jurisdiction over an issue and we were expected to take and did take the lead. This was most prominent in the international arena, for example, with the annual "Tripartite" meetings with FDA counterpart agencies in Canada and the U.K., and with the regular meetings with FDA counterparts from Canada and Mexico.

We helped CDRH with its International Conference of Device Regulatory Authorities and their work with WHO, and we helped CFSAN with their international conferences and their work with WHO and FAO.

The Center for Veterinary Medicine (CVM) had always worked closely with the OIE (the World Organization for Animal Health, earlier known as the International Organization for Epizootics) and was quite effective. We helped them out when requested. An example was when CVM wanted to see if they could learn from and possibly emulate the ICH process. This ultimately resulted in a veterinary ICH.

One important change in OHA's role occurred when Dr. Kessler split off most of our international activities into a separate office.

SJ: I'm really not clear on that transition into a full-fledged international office.

SLN: I'll explain that.

At this time, the international program was growing so large at FDA that Dr. Kessler and others thought it should have its own locus, separate from the Office of Health Affairs. The International Staff in OHA was down one rung in terms of the hierarchy of the FDA bureaucracy. By adding a layer of Deputy Commissioners, Dr. Kessler had already downgraded the position of the Associate Commissioners in the bureaucracy. There were some other issues involved as well. I think Dr. Kessler wanted more direct control over the international program. He didn't believe there should be an Associate Commissioner interposed between him, the Deputy Commissioner for External Affairs, and the international program.. The reorganization put the International Affairs Office directly under the Deputy Commissioner for External Affairs, the same Deputy Commissioner, Sharon Holston, to whom I reported.

My view was that OHA had quite successfully managed FDA's international program. The international program in OHA grew from a small staff to a major unit, and was serving FDA quite well. I was very proud of this and the international ties that I and others in OHA had worked to forge. Dr. Kessler wanted to have it split out, so it happened. OHA retained responsibility for managing two major FDA activities in which I had been personally involved from the outset, from when OHA was established -- coordinating FDA's relationships with WHO and with the ICH. It was understood that these were two major cross-FDA programs that we had handled very well for many years. In other words, it wouldn't be wise to juggle these very successful programs. International harmonization was becoming more and more important as a way to counter

trade barriers, to remove barriers to the conduct of international clinical trials, and to be able to make drug donations, permitting the exportation of investigational and approved products.

We e worked with the Office of Policy on a number of those harmonization issues.

I should mention now that when Dr. Kessler staffed up the Office of Policy under Mike Taylor, one of the new Deputy Commissioners, he charged it with a number of roles similar or identical to those already being carried out by the Office of Health Affairs. While we were much more of an operational than a policy office, many of our activities were a combination of both policy and operations. We did work closely with the Office of Policy, especially on a number of those international harmonization issues.

Linda Horton was our point of contact for this in the Office of Policy. OHA was given the job of leading an agency-wide international harmonization task force that included all the Centers and relevant Offices in the Office of the Commissioner. I chaired the task force which developed a major set of recommendations that served to guide FDA's immediate and long-term international harmonization activities. Linda Horton was quite active on the task force. The Office of Policy, however, was not the new site for the international office

I could not argue with the desire to elevate the status of international programs at the agency. It was a good idea and, in a way, validated the infrastructure and good

relations that OHA had established. I had a and good and close-working relationship with Walter Batts, whom I had chosen earlier to head the International Affairs Staff in OHA, and who was appropriately named the Director of the new International Office. I worked closely with him and his staff in many areas where both our offices had a stake, especially including WHO issues. I continued to be very active personally with WHO, continuing to serve on U.S. delegations to the World Health Assembly and to the WHO Executive Board, and to participate on WHO Expert Committees on pharmaceutical and biologics policy and other substantive matters, such as international drug scheduling, Direct to-Consumer advertising, and Internet pharmacies.

As a brief aside, I didn't mention an additional benefit of international work. There is a great deal of information sharing about the international and domestic programs in the preparation for WHO World Health Assemblies (WHA). Position papers for the agenda items are developed by the Secretary's International Affairs Office or by the most concerned agency, based on the subject matter, and are shared with and cleared by the other agencies that will be represented on the U.S. delegation. You work with representatives from the other agencies on the delegations, before, during, and after the WHAs and learn a good deal about the other agencies' domestic and international programs. Similarly, they learn a good deal about FDA.

I should also add that I was very proud to have received the highest individual HHS award presented at the 1999 HHS Awards Ceremony by Secretary Donna Shalala for my work on behalf of FDA and the Department, primarily because of my WHO-related international activities, especially while serving on HHS-led delegations to the World Health Assemblies when she headed the delegations. Ironically, this happened at

the same time OHA was abolished by Dr. Henney.

SJ: Was that around the time period that they began doing some outreach programs with the Soviet Union?

SLN: These outreach programs began earlier, before the new International Office had been set up outside OHA, before most international activities had been split off. This happened when Dr. Kessler was Commissioner, and not a change that was needed or one that I thought was implemented in an appropriate manner.

Mary Pendergast, who was Dr. Kessler's Principal Deputy Commissioner, had a major interest in Russia and Eastern Europe (the Former Soviet Union -- FSU -- and the Newly Independent States -- NIS). Dr. Kessler decided that she should manage all FDA's interactions with those countries. The Commissioner decided to pull out Russia and Eastern Europe as a special activity that would be entirely managed by Mary Pendergast. I learned about this in a very brief meeting with Mary, not from the Deputy Commissioner to whom I reported. There was no discussion at all, I was just told this is they way it be. To do this, she took one of the best staff persons from our International Affairs Staff, Phil Budashewitz, a pharmacist, as her assistant in managing this program. Initially, it was problematic for our international program to figure out how this would work from a practical standpoint. . I think that Mary was successful in doing a number of things with Phil's assistance, but I wouldn't say that it was a good management approach to suddenly split off one large and important region of the world from the other FDA international activities. While a number of good things happened through Mary's efforts,

there is no way to evaluate any lost synergies that might have occurred had the FSU/NIS remained part of OHA. When Dr. Kessler and Mary Pendergast left FDA, these programs reverted to the new Office of International Programs.

Under Dr. Kessler's regime, a number of things happened that were detrimental to the longstanding strong FDA bureaucracy and team spirit that I had experienced since I joined the agency in 1976. Dr. Kessler was so focused on tobacco that it appeared that he let other issues that were important for FDA and the public flounder or be managed by whoever on his senior staff wanted to be in charge of them. It appeared to us that if one of his Deputies was interested in a particular issue, that Deputy could just take it and run with it, regardless of where it was housed in the organization. Splitting off a major part of FDA's international program was an example of this.

SJ: But we also had three deputies at that point. How did that affect the traditional FDA structure? It was a big change.

SLN: The Deputies presented some real challenges.

At the Policy Board (Senior Staff) meeting where Dr. Kessler announced that he was going to bring in a new layer of Deputy Commissioners, he said to us, "I'm hiring some deputies, and they're going to help you in your work, not interfere with your work." The Deputies came, and it became clear they weren't actually there to help us; they were there to help Dr. Kessler manage the agency in the way that he wanted. There was nothing wrong with that concept. This was a reasonable management approach, if

implemented properly. It was disruptive and difficult. It didn't need to be. It was how it was run, essentially a "free for all." As I said, one Deputy didn't mind taking programs and staff from another, whether it was good for FDA or not.

The problem here was having the Deputies take a major role in running things for which they were not well prepared, not fully informed on particular issues, including at times, even those under their jurisdiction. Especially frustrating was the fact on some occasions, two or three Deputies meeting only with each other , without staff input or participation , were making final agency decisions without the necessary information--not having consulted with the cognizant career program staff.

Unfortunately, that was not uncommon. This actually happened with some important Institutional Review Board (IRB) issues.

SJ: Did they come back to you?

SLN: Sometimes. But the main issue was that not being at the meetings precluded responding to issues raised in the back--and-forth of the discussions. And you couldn't do anything after the fact about decisions already made.

And then, well, there were some other things.

One of the Deputies -- Mary Pendergast, the Principal Deputy --took a real liking to a number of programs that were the responsibility of my Office, OHA. I could understand why she liked them because they were interesting, important, and challenging programs. In addition to the Russia and FSU/NIS activities that she had taken over, she wanted to manage portions of the FDA Human Subject Protection Program, including

IRB and Informed Consent issues. So she assigned a person to help her with IRB issues, Bonnie Lee. Bonnie was quite knowledgeable on many aspects of FDA's human subject protection program and when she worked in OHA/HAPS had been our lead expert in this area. But Bonnie had left OHA to work in the FDA Office of the Executive Secretary in the Office of the Commissioner on matters under their jurisdiction. Nevertheless, Mary had Bonnie work directly for her on human subject matters. They directly handled memos and other documents sent to the FDA Executive Secretary should have been referred to and handled, according to normal protocol, by OHA, the staff in our office that had both the responsibility and expertise to deal with them. The Deputy Commissioner to whom I reported was powerless to intervene and was dissatisfied by the situation, as well.

That was a poor administrative approach, and one that Dr. Kessler either had no knowledge of or didn't care about.

Now, Mary Pendergast was certainly smart and capable, and she knew the agency well from her prior experience in the General Counsel's Office, but that was not an appropriate way to function. And I remember asking the Deputy to whom I reported why parts of programs OGHA had been running were siphoned off. She did not know the answer.

Regardless, the Deputy Commissioner to whom I reported was not able to intervene to get things back into the appropriate channels. In short, in my view, Dr. Kessler's management style was very problematic and detrimental to OHA's and FDA's overall functioning.

SJ: And who did you report to?

SLN: First it was Carol Scheman, and later, when the incidents I just described occurred it was Sharon Holston.

Sharon was a very good administrative person and quickly grasped what she needed to know about OHA programs, but she wasn't able to fight to retain OHA programs (and, of course, her programs, too) that were the target of "takeovers," by two Deputies, Mary Pendergast and Michael Taylor. I can't speak for Sharon and I don't know whether she could have been able to do anything about this, especially if that's what Dr. Kessler wanted, as Commissioner. I certainly asked her to see what could be done about this but things didn't change.

Most problematic was purposely setting up duplicative organizational structures with no procedures for communications among the programs. The Office of Policy, as I mentioned earlier, was the main problem in this respect.

That office was doing some of the same kinds of things that we were doing in the Office of Health Affairs. Dr. Kessler obviously favored certain things being done in the Office of Policy, but we would not know which they were until we heard about them from third parties. Our first Deputy Commissioner for External Affairs, Carol Scheman, was well aware of this, but definitely not helpful in dealing with it. Our second Deputy Commissioner told me she did not understand why Dr. Kessler had done this. The duplicative activities included issues that were the responsibilities of, our Medicines Staff, Health Assessment Policy Staff and the International Affairs Staff.—all of OHA's offices.

I will now mention a problem I encountered with the tobacco program. This is another example of a management problem. As is well known, Dr. Kessler had a large group sequestered to work only on tobacco, which was fine. Staff from across the FDA was detailed to work on this full time. After all, this was a major public health problem.

The problem was that he told them not to tell their supervisors anything about what was going on. It was being run as a strictly compartmentalized program. The OHA detailees to this task force were excellent staff, and we were happy to contribute their time and expertise to this important public health effort.

One day Dr. Kessler called me, and he said he had a complaint to register with me. He told me that he had told a member of my staff to get a copy of a tobacco patent from Brazil that he needed for his tobacco work, and that person did not get it for him. I told him that this was the first time I had ever heard about this. He then told me to get on an airplane that weekend and go to Brazil and get this patent for him. I told him that there was no need for me to do that and if he wanted the patent, I would get it for him directly, but I didn't need to go to Brazil to get it. After I explained how I would get it, he agreed I didn't have to go to Brazil, and within a few days, or at most a week, I produced the patent through the normal channels -- working through the U.S. Embassy in Brazil and the State Department headquarters in Washington. I was able to get what he wanted based on my knowledge and experience in running the FDA international program for many years. Of course, I couldn't advise my staff members about what to do, if I didn't know what they had been requested to do. I saw this as another example of poor management and counter to the agency-wide teamwork that had been the hallmark of FDA. On the other hand, to his great credit, Dr. Kessler was very successful in

managing the tobacco program, no question about that, but it did cause many problems across the agency for the non-tobacco FDA programs, the bulk of FDA's work. Also, I understood that much of the tobacco program had to be conducted as a secret enterprise. It was just that this was an example of a failure to utilize the expertise available to solve a specific, important problem.

SJ: Your experience was ignored for the most part.

SLN: No, but I think I could have been much more helpful in this effort had I been asked.

But given the secrecy that surrounded the program, it's hard to know the correct answer. I had long been involved in tobacco issues at FDA and, when Dr, Kessler was Commissioner, was involved in facilitating coordination of FDA activities in this area with tobacco focal points in foreign governments and worked to engage WHO in a major way. I organized a special tobacco regulatory panel at an ICDRA meeting in Bahrain. We were able to get the WHO Director General at that time to be on a panel along with Mitch Zeller, a key tobacco official at FDA. I think I could have made a more substantial contribution in a number of areas during the process if I had had enough information. Certainly, once decisions were made and they became public, OHA played a major role in the outreach efforts to our constituent organizations.

Unfortunately, during Dr. Kessler's tenure, for the first time in my FDA career, intra-HHS politics became a controlling factor. I was told directly by my supervisor, Carol Scheman, not to discuss issues with two of my Associate Commissioner

colleagues, with whom I would ordinarily discuss issues of mutual interest. The concern, I was told, was that they might share Dr. Kessler's plans with the Office of the Secretary and, if the Department found out about them, they might stop them. Perhaps this was true, but it seemed a sad state of affairs.

SJ: Tell me about Carol Scheman's Office.

SLN: Carol was in charge of the Office of External Affairs. This included a number of offices -- Legislative Affairs, Public Affairs, Health Affairs, Consumer Affairs, Women's Health, and HIV/AIDS and Special Projects.

I don't think it was necessarily Carol Scheman's idea to keep information away from my colleagues but she delivered that message to me. The message was I shouldn't be talking and sharing information with my colleagues, two Associate Commissioners. There was tension. It was no longer a team effort. Areas were being split off and compartmentalized. Now, that didn't mean that we couldn't accomplish a tremendous number of really important things, but it posed difficulties. I mentioned the deliberate establishment of duplicate organizational foci. At times, as I said, others were asked to do work that should have been performed by the Office of Health Affairs. It was all being done behind the scenes.

SJ: Who were you working with during that period? Were people working around Kessler? Was that your perception?

SLN: I guess my perception was that he was not engaged in most of the agency issues and that the Deputies were running things in an ad hoc manner.

I don't know, of course, but I don't think that staff who reported to me, except those on the tobacco task force group, were dealing directly with the Commissioner or with the Deputy Commissioners on issues. I was fortunate in having experienced, knowledgeable, professional staff in OHA who regularly worked together with me as a team.

SJ: And you had fingers in so many different pots.

SLN: We did, both inside and outside the agency. I believe we were a very valuable resource. We were well thought of by our external constituency, domestic and international, and responsive to their concerns, as well as by FDA staff at all levels over the years.

So, yes, there were some constraints on our activities at that point. But overall, I think we were still able to do a good job for the agency.

SJ: Tell me a little bit about how you split up some of the staff responsibilities.

SLN: Our Medicine Staff, the part of OHA that concentrated most on interacting with health professional and scientific organizations, Medicine Staff served as the FDA liaison to the Healthy People program and the Preventive Services Task Force, and to technology and quality assurance programs and initiatives dealt with by HCFA (now CMS) and AHCPR (now AHRQ). The Medicine Staff had major expertise in generic drugs, as well. A lot of the in-depth expertise of the agency in generic-drug issues was in

our office. Of course, CDER was the primary agency locus for the generic-drug issues. Peter Rheinstein and Tom McGinnis who had both worked on generic drug issues in CDER, were especially effective in dealing with the external health professional community on a wide variety of FDA issues. Peter worked with medical groups and Tom with the pharmacy community. I split certain health professional liaison activities with the Medicine Staff-- they would go to certain meetings and I would go to certain meetings. Peter and I often went to the AMA House of Delegate meetings together because there were so many FDA-related reports and resolutions to cover in the meetings. Often these needed to be commented on by an FDA representative at the same time in separate Reference Committees that met concurrently.

And our OHA International Affairs Staff was quite accomplished. We used the regional desk-officer approach, commonly used throughout the government.

After the separation of IAS from OHA, I continued to have the WHO portfolio and worked closely with the Office of the Secretary-level Office of International and Refugee Health (OIRH) and served as the FDA representative on U.S. delegations to the WHO Executive Board and the WHO World Health Assemblies. These were organized by the HHS Secretary's Office. I believe my continued representation was valuable because I had built up strong relationships with many WHO staff and many members of other national delegations to these meetings over the years. I probably attended 13 or 14 World Health Assemblies since I began in 1984, when I began serving on U.S. delegations. FDA was viewed as being the gold standard for drug regulatory authority worldwide, in the '80s and '90s. When I spoke as the FDA representative on the U.S.

delegation, other delegations paid close attention. The Department was pleased to have FDA representation on the delegation because there were always many important pharmaceutical issues. I participated in many, often contentious, negotiating sessions on WHO Revised Drug Strategy draft resolutions and draft resolutions on other topics. Of course, there were numerous biologics, food, and medical device issues over the years, as well.

I continued to represent the agency in international drug scheduling issues, and participated in many meetings of the U.N. Commission on Narcotic Drugs -- at that time they were in Vienna -- as part of the U.S. Delegation.

As you know, the Office of Health Affairs was abolished in 1999, and that's when I left FDA to go to the Department.

SJ: Do you know why the office was abolished?

SLN: In my view, the Office of Health Affairs was a very valuable unit for FDA. I believe the Commissioner was under severe pressure to decrease the size of the Office of the Commissioner and we were a potential target because, on paper, a number of our activities could be carried out by various Centers. In actuality, this was not really the case for many of our activities. For many of the domestic and international issues we took the lead on, having the Office of the Commissioner doing this was key to their success. Maybe our office in a way was viewed as problematic by the Commissioner because we did a wide variety of things for a long time, and had a good and strong relationship with our constituency and had achieved and maintained a high degree of credibility with them.

We accomplished a lot over the years in a fairly independent way under the general direction of a number of Commissioners and Deputy Commissioners.

Of course, I don't really know the reasons for its being dissolved by Commissioner Henney. Salaries for OHA might have been an issue, as well, because many staff members had worked for FDA for many years and had senior GS grades.

I was never told the true reason, except that when I explained to her Deputy, Linda Suydam, that it was not a good idea for the agency to do this, her response was that Dr. Henney was a physician and she could handle the health professional liaison activities herself. That, of course, made no sense since substantial work was needed to provide health professional and scientific organizations with what they needed. To be able to interact successfully with the leadership and members of organizations required participating in meetings outside of Washington as well as frequent phone calls and meetings with Washington office organization executives. This can only be accomplished with at least a modest sized group of experienced health professionals in the Office of the Commissioner.

Although we had problems with how Dr. Kessler dealt with our Office, as I have described, it was Dr. Henney who abolished OHA, a seriously flawed action. Having watched -- and worked with FDA -- until I retired from my position in the HHS Office of the Secretary in 2007, I could not help thinking that having had an Office of Health Affairs during those years would have helped FDA prevent and/or deal with a number of major, very serious and public health problems related to FDA regulated product problems, where the understanding and backing of the health professional community might have been quite salutary. Our office had its finger on the pulse of the health

professional and scientific communities and understood their views and concerns very well. A well-staffed and experienced Office dedicated to working with the health professional and scientific community during that time could have helped in many ways.

For example, the "From the FDA" columns in *JAMA* stopped soon after OHA was abolished. When I left, the columns continued for only a short time. Dr. Henney had turned the writing of the column over to the Press Office. Within six months *JAMA* became dissatisfied with the quality of the FDA submissions and said that they didn't want this column anymore. That monthly column was a tremendous resource and a valuable vehicle for the agency to have.

And even if there were no column, there were other things that we had done with health professionals in the past that could have been done to work with health professionals -- but they were all resource intensive, and required a staff of sufficient size, experience, and composition dedicated to this task. I think the demise of the Office of Health Affairs was a serious loss to FDA, but I am, obviously, biased. It is my view that the Office of Health Affairs was extremely important to FDA. I think the functions carried out by OHA need to be put back into the FDA Office of the Commissioner in some way, but it can't be done on the side. It's a major effort to do this well. I know some of our responsibilities were given to the Office of Special Health Initiatives, other offices in the Office of the Commissioner, CDER, CBER, and others after we left. But you really need a dedicated group that includes one or more physicians, nurses, and pharmacists to do this the right way.

I think the human subject protection educational programs may have suffered somewhat, as well, but I don't know for sure. We had a close and strong relationship with OPRR at NIH and, then, with its successor – the Office for Human Research Protections (OHRP), in the Office of the Assistant Secretary of Health. We discussed potential regulatory and policy changes long before any proposals were finalized to ensure maximal harmonization. We always sought OHRP review of our draft Information Sheets for IRBs, Clinical Investigators, and Sponsors before OHA issued them. I hope FDA and OHRP have a similar close relationship now because harmonization of policies and regulations is critical to the efficient functioning of the human subject protection community.

SJ: And when Bonnie Lee left, and you had gone to the Department, they did hire the agency's first ethicist, Sarah Goldkind.

SLN: Yes, and I met her and have worked with her a bit in my current work as a consultant at NIH.

SJ: But that's a different approach.

SLN: It's an important additional resource.

Having an ethicist at FDA is a good thing.

It would be interesting to know precisely how an ethicist fits into the educational

program, for example, in developing Information Sheets, educational workshops, and interagency harmonization activities. As discussed, Information Sheets dealt with the spectrum of issues related to human subject protection. These Information Sheets were often developed in response to concerns we heard at PRIM&R meetings and joint OHRP-FDA workshops around the country. As I said, we worked closely with the NIH Office of Protection from Research Risks, and when OPRR was moved to the Secretary's Office as OHRP, we continued to work closely with them, as well. We co-sponsored workshops and conferences and spoke on panels together. We worked especially hard to see that everything we did was harmonized between the Department's human subject protection programs and FDA's. It was collegial and there were no major "turf" problems. Our goal was to make sure that things were made as easy and simple as possible for the IRB community. We worked to minimize any differences to the extent legally possible.

SJ: Bern Schwetz began to handle that for a while after he was Acting Commissioner. I think they do a fair amount of outreach.

SLN: Yes. I understand that he did that and that the Good Clinical Practices group does some of this now. I want to emphasize that working closely with NIH OPRR and OHRP was an extremely important part of our job. I remember negotiating many policies and documents with them. We shared drafts to make sure we harmonized to the extent possible, as permitted within current law and regulation.

We always had working well with other agencies as a high priority and interagency collaboration was seen as critical to our success in promoting the FDA agenda.

That became somewhat more difficult in the later years of OHA because I don't think that either Dr. Kessler or Dr. Henney understood the value of these efforts or the fact that a good close working relationship was in no way lessening our ability to advance FDA's position in interagency negotiations. Whatever the reasons, I think the agency suffered because of the difficulty we encountered in trying to do some of the things that we had done in the past to successfully collaborate with other agencies.

I would like to say a few words about how I worked with my FDA Policy Board colleagues.

I think my collaboration with other Policy Board members over the years was almost always excellent. I worked closely with Paul Hile for a number of years while he was the Associate Commissioner for Regulatory Affairs, and with many other ORA staff. In fact, Paul and I had lunch on a regularly scheduled basis. This gave us the opportunity to informally discuss many issues of mutual interest to our Offices. Earlier, I mentioned our close working relationship with the FDA field offices with regard to Laetrile.

SJ: Ruth Merkatz came in around that time, too.

SLN: Yes.

SJ: How was your working relationship with her on women's health issues?

SLN: I worked closely and well with her. There were no turf issues. She was helpful to OHA and I think we were very helpful to her Office. She was always easy to work with.

SJ: And there were some educational components too.

SLN: Yes. We would work together. On occasion, we would co-sponsor meetings with our joint stakeholders. I spent a good deal of time explaining what we were doing to her and made suggestions about groups she might work with. We shared our list of external groups that we worked with. We were operating the way you would expect people to work together in a bureaucracy, where your objective is to carry out the Agency's mission most efficiently and effectively. This was teamwork at its best.

But the Office of Policy, as I said earlier, was a bit of a problem because they often duplicated our efforts, initially without our knowledge.

I would like to say a bit about our harmonization efforts.
The human subject protection issue was mentioned already. Harmonization is extremely important to the human subject protection community. So unless FDA and OHRP, for example, are on the same page with guidance that comes out, either identical or harmonized, the government will cause a big problem for the community of investigators, IRBs, and institutions, domestically and internationally.

I would like to digress a bit and mention another example of OHA's role and its importance. OHA coordinated with the DOD on behalf of FDA a project to see that the

troops in the Persian Gulf War in 1991 would have available the best possible medical countermeasures to the biologic and chemical agents that we believed Iraq had and might use against our troops. What we did was very responsive to this situation and successful, and it's something that I'm personally quite proud of. I recall that this brought me initially into some conflict with Dr. Kessler. OHA worked closely with DOD's Office of Health Affairs to develop and implement an Interim Regulation that involved using the mechanism of a Waiver of Informed Consent for the troops in the Persian Gulf War so that they could receive drugs and biologics that, even though they had not yet been approved by FDA, were considered by FDA to be the best available treatment, protective, or preventive product available. One of these was a drug and one was a vaccine that could be used by DOD to protect the troops during the Persian Gulf War. And the idea was to grant a Waiver of Informed Consent to DOD that permitted informed consent to be waived under a specific, circumscribed combat situation, including the threat condition and location, at the request of DOD, if FDA granted approval for that specific situation. This meant that the Commissioner would need to approve a specific protocol that was submitted to FDA with certain measures and conditions described before this could even be considered by the Commissioner. And we actually did this through an OHA-led intra-FDA task force in a very short period of time, working closely with the Department of Defense and with the Centers. And there were two products that were reviewed and approved under this rule. One was botulinum toxoid, a vaccine, that was an IND product, long used as prophylaxis for laboratory workers, needed to be made available because of the concern about the use of botulinum toxin as an offensive weapon; and the other one was pyridostigmine bromide, which was a drug to protect

against nerve gas that was already approved as a drug for Myasthenia Gravis, although at a different dosage. And we arranged for this to be done.

This was controversial, however. Having "Waiver of Informed Consent" in the title of the Interim Rule made us a "lightning rod" for some military and veterans advocacy groups, some "public interest" advocacy groups, and most publicly, several well-known lawyers, George Annas and Michael Grodin, who considered themselves to be ethicists. They attacked us as being "Nazis" for using soldiers as experimental animals, referring to the soldiers as "Guinea Pigs." We found this to be a shocking charge with absolutely no basis in fact. What we had done was to arrange for the very best treatment available, like the already decade-old FDA Treatment IND; if a product is not yet approved, but it is the best therapy available because satisfactory alternatives do not exist, it should be made available in a controlled system.

What we did was to arrange for those two medical countermeasures to be made available to the troops to protect them. Pyridostigmine bromide had been available earlier and was standard treatment for use by NATO forces. Furthermore, if the informed consent could be obtained, the waiver would not need to be used. It turned out that botulinum toxoid was only was used with informed consent. Pyridostigmine bromide was used per the waiver, without informed consent. The theory behind this program was that you can't permit a soldier in combat not to take what is considered by FDA to be the best protectant or therapy, because if that person succumbs in an attack, then you're exposing the other troops to mortal danger.

SJ: It's a public health perspective.

SLN: It's was a public health perspective, an individual medical care perspective, a force protection perspective, and a national security perspective.

SJ: Did Catherine Lorraine work on that?

SLN: Yes. Catherine Lorraine worked on it, with several others from the Office of the General Counsel. She was very helpful.
Everything we did went through the General Counsel's Office for clearance. Again, we did this rapidly and, as I said, something I was very proud of. We were able to be responsive to DOD in helping to protect our troops in the Gulf in an ethical manner.

SJ: I think Bob Temple worked on that.

SLN: Bob Temple and Russell Katz and others in CDER worked on the pyridostigmine bromide part; CBER staff worked on the vaccine. It was a cross-agency team effort. Unfortunately, it appeared that Dr. Kessler at first viewed our desire to be accommodating to the force protection needs of DOD as potentially subverting FDA's standards for human subject protection. Of course, this view was in direct contradistinction to my view and the view of those on the large cross-agency FDA team that I was coordinating. As I said, I had the exact opposite view, and I think it was one of the highlights of my career, being innovative and responsive in an emergency situation in response to the needs of the country.

SJ: Wasn't it rescinded?

SLN: Yes, eventually. But it's a complicated story and the final result is that a very similar approach is still available through two different statutes and regulations. There were lawsuits and many hearings and studies, a number of which were concerned with investigating the "Gulf War Syndrome" that some thought was due to one of the products FDA had authorized under the Waiver of Informed Consent program. Although the Interim Rule was rescinded, a subsequent statute affecting DOD permits waiving informed consent in situations critical for force protection but only when approved by the President. The requirements of this legislation are now codifed in FDA's Informed Consent regulations as an exception from the general requirements for informed consent.

The Bioshield Act of 2004 created the Emergency Use Authorization (EUA) that deals with this situation (and others) in another way. The EUA permits utilizing the best available medical countermeasures, if not yet approved for general marketing, for biodefense or for dealing with other public health emergencies if certain requirements are satisfied. FDA was given the legal authority to allow it to designate products under an Emergency Use Authorization (EUA). This new FDA authority authorizes the use of unapproved products and the use of approved products for unlabeled uses, under a controlled system with very specific restrictions. Informed consent is not required.

Several of us in OPHEP co-authored a publication on EUA in the CDC's EID (Emerging Infectious Diseases) Journal in 2007 that describes this new FDA authority. (See Appendix.) The article reviews this new authority in the context of earlier FDA policies, actions, and regulations. The article gives some of the history, explaining its similarity in a number of ways to the Treatment IND, and relates the EUA to the use of Methadone Maintenance Treatment for narcotics addiction when methadone was used early on, before there even was an IND and then with rapid nationwide expansion under an IND. It's making the very best possible treatment available in a severe, life-threatening situation. It's not unlike some of the issues surrounding the so-called "compassionate IND" and INDs for emergency use.

Some of the attacks on this program came from people who were basically suspicious of the military. So anything we did that could be construed as assisting the military in their eyes was viewed as unethical or unlawful.

When you work at FDA, you always have some members of the public and stakeholders disagreeing with you or even attacking you when you articulate agency policies. You know you're going to do things that aren't necessarily going to be popular with everybody as you try to protect the public health overall. OHA developed and coordinated much of the drafting of the interim regulation that permitted waiver of informed consent, "Informed Consent for Human Drugs and Biologics; Determination That Informed Consent Is Not Feasible," and was listed as the point of contact for questions in the *Federal Register* publication of the interim regulation as we were the focal point for complaints, as well. In retrospect, the title for this regulatory program, including the use of the words "informed consent" and "not feasible" was true but

potentially misleading as to the main purpose of the program and it led to a good deal of reflex negativity and confusion.

I believe you are interested in our collaborations with CDC, especially on how we worked with them to inform and educate the health professional community about FDA-related issues. I am quite proud of the good liaison relationship we established with CDC. Commissioner Frank Young was very helpful in facilitating this. He went down to Atlanta with FDA senior leadership for a two-day visit to forge a solid cross-agency FDA/CDC relationship. He wanted to match up the various Centers with the activities of CDC Centers to better collaborate across the board and to collaborate on such cross-FDA issues such as human subject protection and communications. This was a highly successful meeting and led to a good deal of productive interaction in many areas of mutual interest. My CDC counterpart was the Assistant Director for Science, Dr. Gary Noble. We were also both made responsible for making sure the collaboration was working, and to keep the respective agency heads informed.

One of the truly ground-breaking things that was of substantial benefit to FDA and came out of that FDA-CDC agreement was the arrangement we worked out with the MMWR (CDC's *Morbidity and Mortality Weekly Report*) that permitted us to preview draft articles that dealt with FDA-regulated products or FDA-CDC activities. For example, when the draft article made statements about off-label uses of an approved drug or recommended the use of a drug not approved by the FDA (for example, one approved for marketing in a foreign country by an FDA counterpart agency), FDA could insert the appropriate language or qualifier so that when it was published in the MMWR, the language would have been cleared by the FDA. CDC had never before made their draft

MMWR articles available to anybody outside CDC, including the Secretary's Office that had been turned down on a number of occasions previously, because CDC carefully guarded its right to publish its scientific findings without any outside interference. They didn't want the Secretary's Office interjecting itself into either into the reporting of the science or its interpretation.

What CDC did was to permit the editor of the MMWR to send early drafts of select articles to be published on Thursday noon the same week directly to our Office so that we could provide FDA-cleared edits. They gave us about 24 hours to review the draft and to modify it as appropriate for FDA. I asked my Special Assistant, Carol Kimbrough to coordinate the FDA review process. Carol, a lawyer who worked on regulation writing in CDER before she came to OHA, handled this in a careful yet expeditious manner, so that we always met CDC's tight deadlines. I do not recall CDC ever not accepting our recommended changes. We often had important edits to contribute. CDC shared the drafts with us for technical purposes, as an important resource to help them make the articles as factually correct as possible in the regulatory area. I do not recall CDC ever not accepting our recommended changes. We often had important edits to contribute. I recently heard that this collaboration between FDA and the MMWR editors is still active, and that is a very good.

Again, I think, it is another good example of our collaboration with other agencies to better serve FDA's mission of public health protection. This is a good example of the value added by OHA.

SJ: And that was particularly important during the AIDS crisis.

SLN: Yes, especially then, since the unlabeled use of approved drugs (off-label use) was often recommended in CDC publications, including the MMWR and special supplements. Sometimes CDC would recommend drugs that were only approved in other countries. And it wasn't just that. How comments on particular products were phrased was important from a regulatory perspective as well as to physicians and to patients in this country, especially to those traveling abroad.

Also, I didn't mention this earlier, but quite independent of the FDA-CDC overall discussions, I was asked to serve on one of CDC's advisory boards. In the mid-1990s I was asked by Dr. Jim Hughes, then the Director of CDC's National Center for Infectious Diseases (NCID), to serve as the FDA liaison to NCID's Board of Scientific Counselors. Traditionally, there were Federal liaison representatives from DOD, NIH, and FDA. The FDA position had been vacant for some time. I agreed to serve as the FDA liaison, and found it a fascinating experience and one that was an excellent platform for furthering FDA's objectives. This was an excellent opportunity to get advance notice and an understanding of CDC NCID thinking about potential new programs and initiatives and to offer advice on them, to be briefed in detail on current CDC NCID programs, to mix informally with CDC NCID staff, and to meet in executive session with the CDC Director. Of course, this was an excellent opportunity to inform both other Board members and CDC leadership and staff about FDA programs and initiatives. These meetings were well attended by NCID's senior and junior scientific staff. The Board made recommendations both to the Director of NCID and to the CDC Director. The

impact of this group, that I would imagine no longer exists because of reorganizations at CDC, was substantial.

Now, one issue on which I recall we collaborated closely with CDC on was the investigation in Haiti into the diethylene glycol poisonings. I was involved in that.

OHA, CDER, and ORA all worked actively with PAHO (the Pan American Health Organization) and WHO on finding out how the poisonings occurred and in helping the Haitians. At the same time we tried to trace back the diethylene glycol to its source. We worked closely with PAHO and WHO on developing a monograph on what had happened and lessons learned. Unfortunately, the monograph wasn't as helpful as it should have been because poisonings with diethylene glycol continued, in Panama in 2006 and, more recently, in Nigeria. Because brokers in Europe were involved in the Haiti episode, I recall that WHO developed "good practices for brokers" to help avoid the situations like this.

SJ: I think the suspicion at the time was that it was contaminated from China, but we couldn't prove it.

SLN: Correct. Now I would like to comment on our collaboration with CDC overall. We worked with CDC on a number of different initiatives and responses to major events. One important initiative was the new program in the mid-'90s on emerging infectious diseases, based on a 1992 IOM report Microbial Threats to Health in the United States, which led to a large new program for CDC.

The Program, known as CISET, was actually overseen by the White House Office of Science and Technology Policy (OSTP). The Secretariat was the State Department and the staff-level coordination was by NCID CDC. Dr. David Satcher, then the CDC Director, was Co-chair of the CISET Working Group on Emerging Infectious Diseases with Dr. Kerri-Ann Jones, OSTP. The work and the products of the CISET group provided the template for much of the biodefense, bioterrorism, and pandemic preparedness initiatives that were implemented after 9/11.

I should mention another stream of work that occurred at FDA. We were involved in bioterrorism and biodefense preparations in the 1990s. It was after Commissioner Young had left FDA and was in the HHS Secretary's Office as a Deputy Assistant Secretary for Health. We worked directly with him and Fort Detrick and other DOD components on medical countermeasures.

RT: And you were working.

SLN: Our office was the FDA liaison for this activity.

RT: Right. That was the Working Group on Civilian Biodefense?

SLN: There are many different things that we did. The point is we were involved in some of the early biodefense preparedness discussions and activities, particularly related to lessons learned from the Sarin terrorist attack in the Tokyo subway. We were involved with some of the early medical countermeasure issues around anthrax well before the

2001 anthrax attacks. OHA was the agency focal point during that period. ORA was quite involved in that as well.

I want to mention a few other major FDA activities that I haven't mentioned yet in which OHA served as the agency lead or coordinator.

One area is the activities OHA coordinated for FDA with the Institute of Medicine (IOM). We were the FDA liaison to IOM on at least two major activities and on a number of contracts, including one on FDA Advisory Committee management. One quite innovative activity at that time was the IOM Drug Forum, which, with a new name, is still meeting. This Forum was the idea of Commissioner Young and the then President of the PMA (now PhRMA) Irwin Lerner. The concept behind it was to provide a neutral venue where FDA, the pharmaceutical industry, academia, and the AMA would have an opportunity to talk together about regulatory and scientific issues and other of mutual concern. The agenda was tailored for each meeting to explore the topics selected. Topics were often what could be done to lessen what were considered by industry to be regulatory barriers in drug development and how to increase the supply of clinical investigators and pharmacologists.. Later the group was expanded to include Medical Device issues and to include the NIH. As the representative from the Office of the Commissioner, staffing the Commissioner, my role was to coordinate the development of the agenda items and to see that the appropriate FDA Center scientific and technical staff participated. I did this by working with the Center Directors from CDER, CBER, and CDRH who were all members of the Forum. That was an important, outward-looking activity of OHA.

The other IOM activity I would like to mention is the IOM Forum on Emerging Infectious Diseases, which also still exists. Again, our office was the liaison, which meant identifying the appropriate representatives from other FDA components. I was part of the group that included CDER and CBER that would help with the development of agendas and participate in the meetings, making sure that we were being as responsive as possible and bring back issues and problems identified for the agency to consider and act upon. This was a very important activity for FDA.

SJ: Tell us a little bit about your work in the Department subsequent to your leaving FDA and going to the Office of the Secretary.

SLN: Do you want to hear about that?

SJ: Yes, but make sure we've got everything from your tenure here.

SLN: OK. I would like to cover some additional OHA activities first. Over the years, in my role at FDA, I was involved in a number of activities with other organizations, government and nongovernment, that I think were very useful for the agency to be involved in. Our Office served as the FDA liaison to a number of committees, groups, and organizations that I don't think I mentioned earlier. Examples of activities we were involved in included serving as the FDA liaison to the Congressional Office of Technology Assessment (OTA) that does not exist any longer. Recent press reports have suggested that an office or agency like that is needed again. We provided a great deal of

information to help them with assessments that related to medical devices and other products regulated by FDA.

We worked closely with the NIH OMAR, Office of Medical Applications of Research, that office that organizes and convenes the NIH Consensus Conferences. I served as the FDA ex officio member of its advisory committee. The Office was initially headed by Dr. Seymour Perry, who did an outstanding job in establishing and running it. There was a great deal of interest in products under FDA's jurisdiction, especially medical devices. It was important to make sure that FDA was properly represented on the OMAR planning committees for FDA-relevant Consensus Conferences that dealt with the use of FDA-regulated medical products. This included the off-label uses of drugs, and reviews of FDA-approved products for the labeled indications, for example, whether drugs or drug classes are safe and effective for specific indications and whether medical devices were safe and effective for cleared or other uses. Examples included Consensus Conferences on the treatment of Attention Deficit Hyperactivity Disorder with stimulants and the safety and efficacy of Electroconvulsive Therapy (ECT). Many of these were important to FDA, and it was OHA's job as liaison to participate in early discussions on potential topics for Consensus Conferences, in the shaping of the questions about the technology selected to be for deliberation by the expert panel, and helping to identify the most appropriate experts to serve on those panels.

OHA had experts on its staff who could serve on the OMAR FDA-related Consensus Conference planning committees. When it didn't, we found the FDA experts who could do this. If OHA staff played this role, I always made sure that the appropriate Center experts were brought into the planning process. The Centers were always

interested and cooperative in this. If FDA is not able to play such a role, then the agency really loses out on an extremely important venue where the indications for FDA regulated products are undergoing additional expert review.

I don't know if FDA has a liaison to OMAR now, but it's something that over my 20-year career in the Office of Health Affairs, we valued greatly and we worked to see that FDA was properly represented which was very helpful over the years.

By the way, FDA was fortunate that for a period of time in the 1980s, Dr. Crout headed OMAR, after leaving FDA.

I didn't mention this earlier, but there was another activity that the Office of Health Affairs led and staffed, FDA's Institutional Review Board (IRB), which was named the FDA Research Involving Human Subjects Committee (RIHSC) that not only served the agency in reviewing intramural and extramural projects that FDA either conducted or funded, but also gave us "real world" experience in following our own FDA Informed Consent and IRB regulations and the Common Rule, the HHS human subject protection regulations. Doing this gave us a perspective that enabled us to better appreciate the problems that IRBs faced, and thus better able to serve our constituency. We were inspected by the local FDA field inspectors. I chaired the RIHSC for five years, in the early-mid 1980's and OHA staff, throughout OHA's existence, provided administrative support to the committee. At national and regional meetings, I talked to many IRB chairs and members about what they did and what their problems were. In a number of cases, because I saw them firsthand and had to deal with the same kinds of things that they had to deal with, I was able to discuss their concerns and potential

solutions with them in detail. As I mentioned earlier, sometimes this led to OHA issuing new Information Sheets to explain how to address these concerns.

Of course, the RIHSC served and extremely important function for FDA since all research with human subjects needed to be approved by this committee before FDA intramural or FDA-funded extramural research could begin. The work of the committee brought us in closer touch with the scientists in the Centers and was helpful to us in understanding some Center activities that we might not otherwise have known about.

I also was the chair of the FDA Medical Officer Peer Review Committee that made recommendations for the promotion of Medical Officers in the various Centers. I got to know quite a bit about how Medical Officers worked and were treated in different Centers. There was quite a disparity in Medical Officer grade levels and decisions about when to propose them for promotion. It was also a good opportunity to work closely with fellow SES-level physicians in the Centers, the members of this committee.

I'm trying to think if there's anything else that I would want to mention.

I guess there is one important summary observation that I would like to make about my experience in FDA over 24 years.

I was talking earlier about how, in my final years at FDA, the collegial attitude and teamwork that had been the hallmark of FDA at the Policy Board level was greatly diminished. This began with David Kessler's becoming Commissioner and his interposition of an entire new layer of management, a layer of multiple Deputy Commissioners who were assigned to oversee all agency programs, but often resulted in programmatic redundancy and a number of poorly conceived efforts.

It appeared that Dr. Kessler largely avoided personal management of the agency overall. He left the various Deputy Commissioners to fight among themselves over who was responsible for what, while it appeared he concentrated solely on tobacco, with great success, of course, in that area.

Most unfortunate was the duplication of effort and the serious disregard of adherence to the normal bureaucratic process, not bureaucratic in a pejorative sense, but bureaucratic in terms of who's responsible for what program, to whom you report – procedures that are essential in managing an established regulatory agency with 10,000 or so employees. What appeared to be the purposeful duplication of effort was wasteful, counterproductive, and bad for morale. Knowingly giving the Office of Policy and the Principal Deputy functions similar or identical to those in OHA were examples with which I was personally well acquainted.

When Dr. Jane Henney became Commissioner, I believe she tried to restore a more rational approach to managing FDA. I had worked with her when she was at NCI in the 1980s and again when she was one of the Deputy Commissioners under Dr. Kessler. During that period she did quite a good job. Unfortunately, after she became Commissioner there continued to be a lack of teamwork and collegiality at the Policy Board level that filtered down throughout the agency.

Is there anything else you want me to discuss about my experience at FDA or shall I talk about my work in the Office of the Secretary?

SJ: Well, tell us a little bit about your subsequent career, when you went to the

Department of Health and Human Services.

SLN: Yes. I went from my position as Associate Commissioner for Health Affairs, to work in the Office of the Assistant Secretary for Planning and Evaluation (ASPE) in the HHS Secretary's office. Dr. Margaret Hamburg was the Assistant Secretary at that time.

SJ: So you knew her.

SLN: Yes. She offered me a position in her office so and I left FDA at that time, initially on a detail. Dr. William Raub, who had served in NIH for many years and then at EPA before returning to HHS, was my direct supervisor in ASPE. I had worked with Bill Raub on human subject protection issues when he was the Deputy Director for Extramural Research at NIH. ASPE was an extremely interesting office. The pace was slower than I was used to because it was primarily a policy office, not an operational one. Drs. Hamburg and Raub asked me to work on and, in some cases, coordinate at the staff level, a number of interesting issues that were soon to become major public health and societal concerns. For example, ASPE was at the forefront of issues like bioterrorism preparedness and response and pandemic influenza preparedness. Dr. Hamburg was concerned about these issues long before they were recognized as being major societal concerns. It was her direct interest in biodefense that led to the establishment of the CDC national stockpile for medical countermeasures. She resurrected work in the Department on the HHS pandemic influenza plan that had languished for 25 years or so. Although others in the Department were not especially concerned about pandemic preparedness,

she forged ahead and, after she left, Bill Raub carried on that effort that, eventually, following global outbreaks of avian influenza and SARS, pandemic preparedness planning gained both HHS and White House support in the Bush Administration. In fact, had it not been for Dr. Hamburg's vision and early efforts, the government would have been ill-prepared for the H1N1 pandemic. The government-wide pandemic influenza preparedness in place when the H1N1 pandemic began was based on preparations to deal with potential outbreaks of avian influenza with human transmission.

I learned a lot about working in the Secretary's Office, how to get things done, from Drs. Raub and Hamburg, and I really enjoyed working with both of them.

The move from FDA to ASPE was a bit tricky because I needed to transfer my SES position from FDA to ASPE. FDA did not want to give up an SES position. It was to be a lateral move within SES after my detail from FDA ended. Because ASPE didn't have a vacant SES position at that point, for me to stay in ASPE, the Secretary had to find another permanent SES position for me. Both Dr. Hamburg and Dr. Tom Novotny, the Director of the PHS International health office -- The Office of International and Refugee Health (OIRH) – encouraged Secretary Shalala to find a permanent SES position for me. She did, and I ended up working mostly in ASPE but also in OIRH as Senior Medical Advisor to the Director. I was very happy with this arrangement since it allowed me to continue to work on a number of important substantive international issues that I had been involved in at FDA, as well as to work on many new ones.

A major activity in ASPE that I was responsible for was planning for and orchestrating the conduct of a conference on Disclosure of Financial Conflicts of Interest and Human Subject Protection. The Conference, co-sponsored by the HHS Office of the

Secretary, FDA, CDC, and NIH, was held on the NIH Campus in the Natcher Auditorium in August 2000 and had over 800 participants. The information we gathered led to our developing a draft HHS Guidance in 2001, "HHS Draft Interim Guidance: Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider when Dealing with Issues of Financial Interests and Human Subject Protection." I was able to stay involved in coordinating efforts to move this draft to a final Guidance even when I transferred from ASPE to The Office of Public Health Emergency Preparedness in the Office of the Secretary. We were successful in issuing a final Guidance, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," in 2004.

I was quite involved with some of the major Departmental activities after 9/11, when bioterrorism became a major Departmental activity.

In 2004, I joined the Office of Public Health Emergency Preparedness (OPHEP), which became the Office of the Assistant Secretary for Preparedness and Response (ASPR) in 2006. OPHEP was focused on preparing for and responding to bioterrorism and chemical and radio-nuclear emergencies as well as on pandemic influenza preparedness.

Clearly, my work at FDA over the years equipped me quite well to deal with many of the issues that I dealt with in the Office of the Secretary.

Throughout my career in the Office of the Secretary, I continued to work almost half-time in international activities. I had a dual appointment, serving in the OIRH and its successor, the Office of Global Health Affairs as Senior Medical Advisor to the Director concurrently with my role as Chief Medical Officer in ASPE. When I moved

into the Office of the Assistant Secretary for Public Health Emergency Preparedness, I retained the appointment in the Office of Global Health Affairs. Thus, for the seven years I served in the Secretary's Office, I was the Senior Medical Advisor to the Director of the Office of Global Health Affairs.

Stewart Simonson, Assistant Secretary for Public Health Emergency, recruited me to be the Chief Medical Officer for OPHEP and to head the Office of Medicine, Science, and Public Health and, soon thereafter, to serve in the position of Deputy Assistant Secretary for Medicine, Science, and Public Health, in addition to being the Chief Medical Officer for OPHEP. I very much enjoyed my almost three years' time in OPHEP/ASPR. I continued to work a lot with many agencies throughout the Department as well as with other Departments and the Executive Office of the President. And I found that period to be an exceedingly interesting and fulfilling part of my Federal career. Working with Stew Simonson was a great opportunity. He was enthusiastic and action oriented. He had many good ideas and because he wanted to get things done, I was able to help him to accomplish a great deal, utilizing skills I had developed over the years at FDA and ASPE as well as in the Executive Office of the of the President to coordinate efforts across agencies to get results. Stew Simonson had developed exceptionally good working relationships with the leadership of across HHS, including the FDA Commissioner, the Director of CDC, NIH and NIAID Directors, as well as with the senior people in the Office of the Secretary, many of whom he had worked with on Secretary Tommy Thompson's staff when he was the Governor of Wisconsin. An especially important relationship was the one between Stew Simonson and Bill Steiger who were already colleagues before joining HHS. Bill had become the Director, Office of

Global Health Affairs and was the Special Advisor to the Secretary for International Affairs. He, like Stew Simonson, was action oriented and, working together, they accomplished a great deal internationally. Since I had positions in both offices I was often able to work directly with both of them concurrently to facilitate swift the implementation of numerous projects and actions. Both their offices and mine were all close together on the sixth floor of the Humphrey Building.

Examples of some of the FDA-related issues I coordinated from the Office of the Secretary included developing Department-wide positions on the World Medical Association's Declaration of Helsinki that I first worked on with Bob Temple in the mid-1990s while at FDA. (In fact, I continued to work on this issue as a consultant at NIH, starting in 2007.)

Coordination of HHS policies on international drug scheduling, an activity that OHA coordinated for HHS for many years, was taken over by OGHA while I was there. I played a facilitating role in the discussions of specific products and suggested strategies for HHS positions to be taken at WHO and the UN Commission on Narcotic Drugs. These recommendations were informed by my experience serving on US delegations as well as on WHO expert committees for about twenty years while I was at FDA overseeing these activities in coordination with OIRH, DEA, NIDA, SAMHSA, and the Department of State. Of course, my work on developing US positions for WHO Executive Board and World Health Assembly agenda items, involved my consideration of FDA activities and policies.

There were several other initiatives that I was involved in that brought me into close contact with FDA while I served in OPHEP/ASPR and OGHA that I want to mention: the first was the EUA program that I discussed earlier. FDA was designated in legislation as the lead agency for the determination of which products actually were designated as EUAs, but an elaborate coordinated interagency process was involved in preparations for the ultimate FDA determinations. I chaired the OPHEP/ASPR EUA Steering Committee that Stew Simonson had wisely established that included representatives from the Department of Homeland Security, DOD, VA, HHS/OS OPHEP, Office of General Counsel, CDC, FDA, and NIH. The EUA Steering Committee's job was to see that the system was working properly to tee up products that that should be moved through the pre-EUA process and made available quickly in an emergency. Representatives from the FDA Office of the Commissioner and Centers served on this policy and operations committee. We developed a "playbook," an operations manual that outlined timelines, procedures to be followed, and roles of each agency when an EUA was being considered under a declared emergency. My experience with such issues as the Treatment IND at FDA was very helpful in addressing EUA concerns.

Another FDA initiative in which I was involved in the Office of the Secretary, I believe made a very substantial contribution to treatment of HIV/AIDS patients in countries that were part of the President's Emergency Plan for AIDS Relief (PEPFAR) countries and inspired other innovative programs.

This joint HHS/OS-FDA program to grant "tentative approval" of HIV/AIDS products submitted in association with the PEPFAR program that was began in 2004 was initially co-coordinated by the Immediate Office of the Secretary and OGHA. Under this program "tentative approval" was granted to generic formulations of approved but on-patent HIV/AIDS drugs that could not be marketed in the United States until their patents expired so that they could be purchased with U.S. government funding for use in PEPFAR countries.

The OGHA AIDS Coordinator, Dr. Michael Johnson, was the lead in the implementation phase with FDA. I helped in that aspect but was mostly involved in the conceptual and strategic phases, working closely with Ladd Wiley, Counselor to the Secretary, who was the overall Departmental lead for this initiative. I worked directly with Bill Steiger, Stew Simonson, and Phil Budashewitz, then in OGHA, and a number of dedicated and enthusiastic FDA CDER international (Justina Molzon) and Division managerial and review staff (Debra Birnkrant, Leonard Sacks, Mark Goldberger, and Gary Buehler).

This program was an entirely new initiative for FDA but relied on many extant FDA activities: The same level FDA review for safety, efficacy and quality for marketing approval in the US and FDA worked closely with companies that may not have submitted applications to the FDA in the past to assure the applications were properly prepared and the manufacturing facilities were ready for FDA GMP inspections. Sometimes this required advice on specifications for new manufacturing facilities.

The Office of the Secretary and FDA worked with generic firms in India and South Africa, many of which had never submitted drugs for marketing approval to FDA. Marketing applications were given priority status and reviewed quickly. Registration fees were either not required or waived, depending on whether the products were new drugs or generic drugs. Also, the tentatively approve drugs were quickly placed on the WHO pre-qualification list, giving them a much broader imprimatur that was important to many developing countries.

This new program was implemented though the development of a Guidance for Industry. The program permitted the approval of fixed dose combinations of drugs that were never submitted as fixed dose combination products to FDA for approval.

In order to describe our proposed plans, gain acceptance, and understand the concerns of the drug regulatory agencies in Africa, we jointly planned and convened conferences in South Africa and Botswana in close cooperation with the Southern Africa Development Community (SADC) FDA counterpart national members and the Director of the dug program at WHO, the same person at WHO was responsible for implementing the new WHO prequalification program for HIV/AIDS dugs, Dr. Lembit Rago. I should mention that Dr. Rago's enthusiastic cooperation between FDA and WHO enabled this program to succeed The key was that FDA tentatively approved HIV/AIDS dugs were listed quickly on WHO's list of prequalified drugs because of the exchange of information enabled by the confidentiality agreement between FDA and WHO.

An important public validation of the importance of this program came in October 2009, when PAHO held a celebration in honor of the 100th HIV/AIDS drug authorized by FDA under the PEPFAR/FDA program.

Another activity involving FDA I want to mention is the preparations HHS made to provide additional influenza vaccine during the 2004-5 influenza vaccine shortage due to regulatory violations by a major vaccine supplier to the U.S. market. Assistant Secretary Stewart Simonson asked me to take the lead in HHS to coordinate a Task Force composed of representatives from HHS/OS (Other OPHEP/ASPR Offices, ASH, and ASPA), FDA, CDC, HRSA, and CMS. Our job was to arrange for a supply of unapproved influenza vaccines from foreign manufacturers that FDA would be able to deem as safe and effective if needed for use under Treatment-type INDs. The vaccine would be imported into the U.S only and be used if the extant domestic supply of approved influenza vaccine was completely depleted. Of course, CBER was a major player in this and was consistently responsive. We not only arranged for the INDs but also organized a distribution system and coverage and reimbursement contingencies for vaccine that would be used under these conditions. Although we never needed to import the foreign influenza vaccine supply that was available under INDs, several foreign manufacturers with whom we had worked during that crisis period, having invested in meeting FDA requirements for this contingency program, decided to enter the U.S. market in future years. This actually happened and provided the U.S. with additional sources of influenza vaccine -- an important gain for public health, assuring a larger annual supply of influenza vaccine. Our Influenza Vaccine Shortage Task Force received

an award from the Secretary. Dr. Karen Midthun, CBER Deputy Director, was among those receiving the award.

One final activity that was a major one for me in my OPHEP and OGHA roles involved FDA as one of the many HHS agencies (and other U.S. government Departments and the White House) with whom we worked. This major activity was the iterative development over several years of the U.S. position on revising the WHO International Health Regulations and overseeing the negotiations with the OGHA Director, Bill Steiger, and the Assistant Secretary for Public Health Emergency Preparedness, Stew Simonson. FDA was an important player in this because of its concern about and role in responding to public health emergencies of international concern that were the result of natural, accidental or deliberate biological, chemical, and radio-nuclear events. This includes pandemics, and relates to all the product areas that FDA regulates and the approval and use of medical countermeasures to all these threats. Having the revised IHRs in place was critical to the pandemic influenza response globally.

I think that completes the major post-FDA activities that kept me in contact with FDA issues and staff while I was in the Office of the Secretary.

Twenty-four years of my career were at FDA, and I have great fondness for the agency and the staff. I would like to see FDA prosper and come to grips with some of the many things that it's facing currently. I can't help thinking that had there been an OHA in FDA over the past decade, FDA would be stronger and the public better protected.

SJ: What do you think of the idea of establishing overseas offices?

SLN: I think it's a good thing. That idea came up often while I was at FDA, but it was quickly rejected because of the cost.

Should we have an international presence? Everyone always pointed to USDA, with its large overseas staff, as a possible model, and the answer was always no. And then all of a sudden, given some of the serious safety problems that originated overseas, the answer became not only yes, but yes in a big way. So I think it's good. I think it's going to be very helpful, but the answer will come when we see how effective the program has been.

And there are extremely competent people, I know, who have been assigned overseas. I worked with Chris Hickey, who is now the senior person in China, when we both were in the Office of Global Health Affairs in the Department. I worked closely with Lou Valdez when she was in several different offices, most recently in OGHA, who now heads the FDA international program office. She has a wealth of international experience in different offices and will have a major role in managing this. I know many of the FDA headquarters international Programs staff and they are quite a capable group. Many are the same people I worked with when I was the Associate Commissioner for Health Affairs.

I know, working with ORA over the years, that it can be challenging at times to coordinate the work of inspectors and non-regulatory policy and program staff, which will be especially important in achieving success in this new FDA overseas program. I'm sure they will all work closely together and avoid problems. I have great respect for the ORA inspectors and for ORA as an organization, and for the staff in the international

program office. And I have great respect for Dr. Hamburg, who will be the one who must ensure that this new program works. The potential for public health protection is substantial, for saving FDA resources through cooperation with foreign governments -- strengthening and, in some cases, building their capacity to carry out inspections in their own plants -- makes this a potential win-win situation for the U.S. and the public in foreign countries with the FDA offices. I'm sure this is what Dr. Hamburg wants.

SJ: Well, it makes this interview all the more timely. I had no idea that you worked so closely with Dr. Hamburg -- you clearly have more experience with her than anyone else at FDA at the beginning of her tenure.

RT: We really appreciate, Doctor, your participation in the history program. Thank you very much.

SLN: Well, thanks for inviting me. I did have a lot to say about my experience, as I was in FDA for 24 years. I did see a lot from a senior agency position that was a fascinating one. I believe I spent more years, 1980-1999, on the FDA Policy Board than anyone else did. Because Office Health Affairs responsibilities spanned the entire agency, we were involved in many interesting and challenging issues, both internally and externally, and domestically and internationally. It was a great place to be. I really enjoyed working with the FDA staff, of course including both of you, while I was there. And, as I said, my experience in FDA helped me tremendously in my later work in the HHS Secretary's Office for the seven years prior to my retirement from the government in 2007.

END OF INTERVIEW