History

of the

U.S. Food and Drug Administration

Interviewee: **Janet Woodcock, M. D.**

Interviewer: **John Swann, Ph. D.**

Date: **26 March 2024 and 22 July 2024**

Place: **Silver Spring, MD**

Index

[Editor's Note: The following preamble to the oral history was requested and prepared by Dr. Woodcock]

This narrative, by its very design, has been about me and the work I've done over the years. But in some sense, it is a false narrative, or an incomplete one, because I did not do this work alone, and in most cases was not the primary contributor. Many people contributed to each of these efforts: agency staff, contractors, people from other parts of government both state and Federal, academics, scientists, patients and patient advocates, members of regulated industry, legislative staff and legislators, and other folk around the globe. We were all collaborators, co-conspirators, planners, plotters, strategists and worker bees. My usual role was instigator-in-chief: envisioning the project, working on how it would be structured, recruiting leads, cheerleading, harassing, persuading, driving, regrouping, encouraging, mediating, urging patience, placating, and generally overseeing things to completion (or not, some efforts failed). And since so many people have been involved, there is not space to mention each of them and their contributions. But I have always held that it is the work itself that is the reward, not the rewards you might get for doing the work.

So I would like to thank everyone I worked with over the years. While routinely maligned in the public sphere, civil servants are among the most dedicated and diligent workforce to be found anywhere. FDA staff, in particular, are completely passionate about its mission (sometimes to a fault, making it hard to envision changes). It has been a privilege, and great fun, to work alongside such very bright and committed people, trying to improve the lives of those who are suffering illnesses, and prevent the healthy from encountering harm. Through all the crises and controversies, the North Star of that mission shone through, uniting us even though we might disagree on the way forward. Collectively we have succeeded in very many ways, improving policy and processes, implementing new ones, and

always contributing to the health and safety of those we serve. It has been quite an effort, and I enjoyed every minute of it.

JS: This is another in the ongoing series of FDA oral histories. The date is March 26, 2024 and my name is John Swann of the FDA History Office. I'm here with Dr. Janet Woodcock on the campus of FDA in Silver Spring, Maryland. Dr. Woodcock, thank you so much for agreeing to do this.

JW: Happy to be here.

JS: So let's, I guess let's begin where you began. Could just take a little bit of time to talk about where you grew up, where you went to college, and any influences that were meaningful to you in terms of going into the sciences and medicine for that matter? And I don't know if that came from parents or others.

JW: Sure. I grew up in rural Pennsylvania in a little town in the Appalachian Mountains called Hollidaysburg, Pennsylvania. And that was an idyllic place to have a childhood for someone like me who loves to be outdoors and loves nature. It was the era where your parents kicked you out after breakfast and said, “be home for dinner.” And so, yeah, I got into many serious scrapes and life-threatening conditions, but I survived my childhood and really thoroughly enjoyed the whole time.

When I was in high school, my father was a small-town lawyer, but he was very interested in education, and he pushed to have the high school have advanced courses. And they had an advanced biology course, and so I took that. I was also very interested in the sciences. And they asked us to do science experiments. And so my friend and I built an electrophoresis machine, and we got blood from different creatures, like we went to the fishery and got blood from fish. We went to the – you can do a heart puncture of the fish without killing it, interestingly. We went to the butcher and got different mammal blood and

a little bit of human blood from somebody. And then we got rid of the – hydrolyzed it, and then we did an electrophoresis of hemoglobin to show that different hemoglobins were different.

And I think that the teacher was so surprised by this that we entered that in a state science contest, which we won. Probably other people won, too, but I don't remember the details. So then I got to go to a science symposium at Princeton.

JS: And what year in school were you?

JW: I was a senior in high school, yeah. And, but I was already interested in science. I wanted to be a biochemist. I decided I applied to different colleges, but Bucknell offered me – I had like a merit scholarship and offered me additional money so I could go to Bucknell. So I went to Bucknell University, and they had a very rigorous chemistry program. And I took like a double major worth of courses in chemistry and biology because they didn't offer a biochemistry degree at the time. So I took all the biology courses.

I spent a lot of time in laboratories, which, nature girl, this made me quite unhappy. But anyway, I got a degree in chemistry from Bucknell. And then I didn't know, that was during the Vietnam War protest time. I didn't really know what I wanted to do afterward. I took some time off and I worked. I lived in Wisconsin for a year working for a biological supply house. And there, the workers, not me, I was like the tech worker, but they were workers in a warehouse, unventilated. And they were bending over vats of formaldehyde every day without any protection.

JS: What did the supply house supply?

JW: Well, they supplied like to schools, fetal pigs that were preserved in formaldehyde, those type of things. And I was the one who did the live stuff like amoebas. And, you know, I had to fertilize frogs and then send fertilized frog eggs to, you know, to schools. And then they'd watch them turn into tadpoles, I suppose.

But anyway, so I told the workers this was unacceptable and they needed to have protection against formaldehyde; it was a known human carcinogen. And they went to management who refused, and so I encouraged them and they got into a union. So then I was fired. They determined I was part of management and I wasn't, and so I was fired from that job. And so I was very poor for a while. And then I moved to Chicago and I got a job as an analytical chemist at A.B. Dick.

JS: This is the office, like an office machine company?

JW Yes, they did printing, yeah, of different kinds. And they made ink and things like that. And I was in the research laboratory because they were always trying to improve things, including their testing for the inks and everything, which are very hard to test because they're all, you know, gloppy.

So I did that and I was bored out of my mind. The clock time is really relative. Time had never moved so slowly. So I got it in my head to apply to med school. And I went and took the MCATs, which you have to do. And then I applied to Northwestern, which was in Chicago. And I applied to Duke, and I didn't go down to Duke. They had an alumnus interview me and he said, “well, you might get pregnant.” Yeah, this was a long time ago. And he said, “well, what do you think of that? You'll never practice. It'll be a waste of a slot.” He literally said that to me.

JS: So did that take Duke off the list?

JW: They took me off the list. I didn't get into Duke, but I got into Northwestern, and that was very helpful because as an Illinois resident, I was eligible for a lower – it was a state-supported school. I was very poor, so I really didn't have to pay much. I took out some loans, but I was able to go to Northwestern.

JS: Wow. So when you started at Northwestern, did you have any kind of future path in medicine you were interested in?

JW Well, all during that time, I thought, well, you know, I really don't like cities, and I really would like to get, maybe I'll become a family doctor and go back and live in Pennsylvania and practice as a family doctor. Right. And that stayed. I finished at Northwestern and I applied to family medicine programs in the Northeast. And I matched with Penn State, which was my first choice, at Hershey. They had a pretty strong family medicine program there.

And so I went there, and it was very good to do a rotating internship and learn all about ENT, and I delivered lots of babies. I had to do all this stuff, you know. But the month in the neonatal ICU, it was like, I can't do this. I can't do all these things. I can't be all things to all people.

So they had a pretty good internal medicine program. I transferred into internal medicine and spent the next several years doing my residency in internal medicine.

JS: Right. Did a faculty position accompany that?

JW No, this is training. Then I was chief resident for a while, which is sort of a resident position, but you help run the program. You have to run the codes when you're in the hospital and stuff like that. And then I stayed in the faculty for a while. That was because my husband was finishing up his doctorate there in molecular biology.

JS: At Penn State?

JW: Yeah, Penn State, yeah. So I stayed there until he finished. That was maybe a year plus, maybe a year and a half or something like that. And I stayed on the faculty. I wrote a chapter in a book they wrote on general internal medicine.

I took over. One of the faculty went on sabbatical and he had an allergy clinic. I took over his allergy clinic. I learned a lot from that. I became interested in rheumatology because they didn't have any rheumatologists. So I took a lot of those patients and treated them. I also made some unusual diagnoses, both when I was a resident and then as a –

JS: Unusual in what way?

JW: Well, they were rare conditions that were rheumatologic conditions. Adult Stills disease. So I diagnosed a case of that. Something at the time was called Churg-Strauss disease, which it's not called that now, but that's what it was then. It was vasculitis. So that piqued my interest.

And rheumatology is something that has a lot of mysteries to it. So when my husband then decided to do his postdoc at Stanford, so then I applied for fellowships in the Bay Area, California. And I interviewed with the Stanford people for health policy. It was quite

interesting. But I was not their first choice. And so I took a fellowship in UCSF with the people there in rheumatology. And I did that fellowship. And then Stanford went and told me they wanted me to come. I said it was too late.

JS: So you obviously considered health policy.

JW: I did.

JS: Is that an interest you've had all along?

JW: Yeah, well, as you probably know, about me, I am a person who wants to make systems run correctly and effectively. And it was clear to me that medicine, they needed a lot of help, right? And that seemed very interesting. It was more about evidence generation, this particular fellowship, and things like that. So I was always quite interested in that.

So then I stayed at UCSF after I finished my fellowship. They asked me to stay. And so I was staying as a junior faculty member there and doing laboratory research, which obviously I was qualified to do since I'd done all this laboratory work. And I was teaching and I was taking care of patients, which I always liked very much. And I had been doing that all the time, of course. And then my husband decided to come to NIH.

JS: You're at UCSF at a very interesting time. Of course, this is in the middle of the AIDS crisis.

JW: HIV, right.

JS: Yeah, absolutely. I mean, that must have been an interesting place to be in the middle of practicing medicine at a place like UCSF.

JW: Yeah, and of course, virology was of great interest. My husband's a molecular virologist. And so, yeah, it was. And it was a tough time for many people. A lot of my patients were gay men and they were seeing, they were terrified and seeing so many people die and be ill and everything. It was a very tough time.

So anyway, then when Roger moved to NIH, I came back. I had just had a child. I had a three-month-old infant, who was a very bad baby. A very tough baby. And so when I moved back, in the midst of all this, I inquired at NIH. I couldn't go along with the kind of, you know, it didn't fit my research interests, the research they were doing then. Some of my grants would have transferred, but you know.

So after a year, when my child was like a little bit more reasonable, I felt I could trust her in other people's hands, I cast around for, looking for a job. And I talked to CDER. And they, they said, we had, they had three people working on HIV. And they said, we have enough people working on HIV. So, because some, my research had involved monoclonal antibodies, people suggested to me that I talk to CBER. And I did that. I went over and talked to the Division of Biological Investigational New Drugs, in CBER. And they said, “oh yeah, we need somebody like you. We need more clinical expertise.” And so I started there on a part-time basis, as a reviewer.

JS: As a medical officer?

JW: Yeah.

JS: Yeah. Reviewing licenses, license applications.

JW: No. They, CBER had a very peculiar system that was based on their tradition at, when they were part of NIH and so forth. So, when they had a license application, they convened people in the laboratories to review it. And, they had a reviewing committee, I forget what they call it. And, there would be somebody from the laboratories who would be the lead. But this was during the biotech revolution, and CBER had a large number of innovative products, cytokines and some monoclonal antibodies. And, so the IND Division oversaw, both administratively and to a great extent, scientifically, oversaw the IND work, the IND development work.

So, that was how it was when I came. I also, as you've probably heard me say, they, when I came, they had a spiral notebook. And they had an individual, one of these support staff, who was very meticulous, would enter each IND application in the spiral notebook, and then each supplement. They were not tracked on a computer.

JS: This is 1986, 87?

JW: 1986, yeah.

JS: Wow.

JW: 86, 87. Okay. Yeah. So, I got, they closed off a hallway in the Parklawn building, and they got a huge old desk from the loading dock, right, which they got their furniture from. And, I was set up there.

JS: So, it's interesting because so much of the CBER was on the NIH campus.

JW: Right.

JS: This part of it, though, was in the infamous Parklawn building.

JW: Right. Yeah, because these weren't laboratories, these units. So, across the hall from us was the licensing division, and they handled the license applications. And, so, Mike Beatrice was the head of the licensing group, if I recall correctly, and Bruce Burlington was the head of the IND group. At the time.

JS: So, okay. You actually moved, moved around within the division, though, pretty, pretty soon.

JW: Right.

JS: You started to, you pretty quickly became a team leader, I think, in vaccines and allergenics. Is that right?

JW: I've had many, many jobs at the Agency. What happened is that, yeah, of course, eventually I could go full time, as my daughter became a little bit more mature. And, then, you know, I was, the thing is that CBER had a model with a lot of PhDs, and the IND phase, you know, the manufacturing is about the product quality, but the rest of it is about clinical evaluation. And they had very few clinical people there.

And I had been involved in clinical trials, and so forth. I mean, and so, I had a lot of medical skills and background to bring to this whole endeavor. So, I, probably, quickly assumed more management positions. And, eventually, Bruce went off, I think, to be Deputy Director of CDER, or something like that. And, then, I became Director of that division.

JS: Right.

JW: Yeah, at some point.

JS: Right. I know things started to change in ‘92 or so, but before going to that, I'm just curious, these first four or five or so years in the division, it wasn't – it was actually the Center for Drugs and Biologics at the time you started.

JW: It was.

JS: And then, so that changed, of course. Not that, well, it did change a few things.

JW: Right.

JS: Administratively. But, do you have any recollections of really, what kind of formative experiences you had when you came into FDA? I'm kind of curious, at that time, how did they prepare people like you to come in? Being that you obviously had a tremendous amount of experience, whatever the normal training system would be, maybe that was just set aside?

JW: Well, I don't think the, the biologics people had much thought for clinical expertise, right? They were really very much laboratory based, a lot of them. Although, they had physicians such as Carolyn Hardegree, and Paul Parkman was the head of the Center for Drugs and Biologics. They were physicians, but physician researchers. There was no orientation, that I recollect. I just got in this hallway with this giant desk and this giant monitor with an old computer. Bruce was very helpful. I mean, he told me a lot of things, but, you know, I said, well, I never heard of the (CFR (Code of Federal Regulation)]. I said, "what's the CFR?" So they gave me some volumes of the CFR to look at and, you know, I just had to talk to people and figure it out. I mean, some of the experiences I had were like, okay, people put forth an HIV vaccine that was going to go into the phase one trials, right, and one of the major news media wanted to have a story on it. So they wanted somebody from the Agency to talk about it and it was a therapeutic vaccine, not a preventive vaccine. They wanted to see if they could boost, you know, immune response.

And so, everyone at CBER said, well, I think Janet is the person who should do this, so I did it. And later, for example, someone had to go down and talk to the secretary, who was Louis Sullivan who was a very good guy, about polio neurovirulence, which is when polio vaccine, the live polio vaccine, would revert and, you know, you can see what that is, yeah. So, and how it was tested for and this and that and the other things, so, well, who should do that? Well, Janet should do that. So it was probably early recognized that I knew how to talk to people.

JS: Had you been asked to do things like this in other positions you had before you came to FDA?

JW: Always. I've always been nominated for different leadership positions and served very reluctantly. It's not, but that was true in many places and many previous things I've been in. Although certainly not working in a company as an analytical chemist.

JS: But as you said, that was almost a miserable experience.

JW: But I helped a lot of people through med school, through the first two years of med school. I'll never forget, it was a time when I remember, they had only had a certain kind of person and that was the med school and it was the time, it was around the Vietnam War and all those different changes in society and they said, we have to have more different people in med school. So they got people who hadn't had the basic prep courses.

I'll never forget, we had a pharmacology course and somebody in the back raised their hand the first day and they said, what's the little d in front of the X? Okay, that means that person had never taken calculus.

JS: Wow.

JW: So I took meticulous notes in med school and they were shared around with everybody.

JS: How do you get through the MCAT if you don't know something like that?

JW: Well, maybe they took people with relatively low scores. I was always good at tests so I'm sure they didn't know me, they didn't really interview me, I don't think, very much. But I had really, my scores were off the wall because I hadn't heard from them and so I called and

I talked to the clerk, she said, oh, well, we're pretty much done with everything. She said, well, let me get your file. And she said, “oh my God, your scores, well, we need to look into this.” So that's how I got into med school. Somebody pulled my file.

But, you know, they had tried to have more of a range of people and so I don't remember that the MCATs then had any calculus on there.

JS: Maybe not, but it's hard to do things like physical chemistry and other things without knowing.

JW: Yeah, well, pharmacology, and it was the pharmacology course that this person just didn't have a clue.

So, anyway, yeah, I helped a lot of people during that time because, except for things like the neuroanatomy and things like the human neuroanatomy, I had covered most of this material in my very extensive training beforehand. But, anyway, that was CBER. They asked me to do a lot of things.

JS: Right, and obviously you were comfortable with that. Perhaps unwilling, but obviously comfortable.

JW: Yeah, I was definitely comfortable. It was nice meeting the secretary. He was very down-to-earth and good and understood it and everything. It was so different than now. I just went down to the Humphrey building, walked in his office, and I'm here to see Dr. Sullivan. Went in his office, two of us sat down, talked it out, and I left. No briefing book, no slides, just like scientists to scientists.

JS: Doesn't happen now, huh?

JW: No. But there were many things like that, and eventually I was on different licensing committees and I was able to see these biologic license committees where they reviewed the application. I was on some of those and was able to see they really didn't have enough clinical expertise, clinical methodologic expertise.

JS: Interesting. Things obviously change in 1992, the Center goes through a reorg, and there were a number of shuffling of offices, but one office came along that you organized, the Office of Therapeutics Research and Review.

JW: Right.

JS: I wonder if you could tell me a little bit about how that came about. This office in fact had a couple brand new divisions if I remember right. Why did they create this office?

JW: Right. Well, the biotech revolution was in full swing then. And don't forget the biologics group had forever reviewed allergenics, which were mainly old timey, like grind up cockroaches and stuff, then blood products, and vaccines. That's what they regulated. And all these new therapeutics, this is totally new. I mean, there's an algorithm for kind of vaccines, what you do, right? Blood products are a whole different world of how they're done and so forth. And they regulated blood banking as part of that and that was a huge issue. The therapeutics were new and so the approach that CBER had been using wasn't going to work for the new products.

So, and particularly it was the lack of the toxicologic and clinical evaluation that was needed. So, we set up, and administratively, you know, we couldn't have spiral notebooks anymore. We needed a very well-oiled machine because applications were pouring in for monoclonal antibodies, for cytokines, for related type of products. And so, and we needed to have policies and we needed to have clinical evaluation and so forth. So, we set up clinical review and we set up toxicology review and then the administrative part, you know, the product quality, how you look at the cytokines and so forth, or whatever they were, that was done in the lab, still in the lab, by the laboratory folks.

JS: Okay. Right. So, I want to say something else about what's going on in '92. So, the Prescription Drug User Fee Act is passed in that year. And, of course, that creates a lot of need for changes in the way we do things in the FDA, certainly in a couple of the centers, in the Center for Drug Evaluation Research, but also in CBER.

JW: Right.

JS: Now, I know you got very closely involved in looking at the way, I don't know if the right word is workflow, but how the review flow is done in the Center.

JW: Yes.

JS: And, you came up with a system of, I think you called it managed review. So, how did you help CBER adapt to the requirements of PDUFA?

JW: Well, it was clear, and that was really part of the founding of the Office of Therapeutics. They had the administrative side of getting all this done, and including the licensing part, so that was changed. And, PDUFA put in place timelines and requirements and communication requirements and so forth, but mainly timeliness requirements. And so, managed review is not very complicated. It simply means that you have a framework in time and deliverables in which you do things. And, especially, you're doing it over and over again all the time. Okay, so, by 30 days, you get back to the sponsor on this, or you have a filing decision to be made in X number of days, and that means you have to count back and decide when you have the initial meetings and so forth. And, this is not rocket science, but they just didn't do stuff like that, really, before.

JS: No, they didn't, but how did the Center adapt to this, this new requirement?

JW: Well, they had the reorganization and the Office of Therapeutics didn't have a lot of trouble, because, don't forget, we were having applications pouring in, and we had to put in place a management structure to deal with that, and so we did so. And we had things computerized by then.

JS: You mean they weren't on spiral notebooks anymore?

JW: No, spiral notebooks.

JS: That's okay, you would get to those in a future assignment, and we'll talk about that. Right, so obviously, there's not an option to fail here.

JW: Right.

JS: You have to keep up with the clock, right?

JW: That's right. But we had to have the relevant expertise to look at these things, because much of it was, okay, so you have a cytokine here, okay. But then you do a clinical trial and you have to evaluate, was that designed properly, did it have the right end points, was it statistically valid? So, we needed statisticians. There were some. In the early days of the biotech revolution there were some bad outcomes. For example, they gave people tumor necrosis factor, which seemed like "oh, that sounds good," right? Well, they gave them a little bit too much, and they didn't too very well. So we had to have that safety before getting into humans, and then evaluate safety during the experiments, and then evaluate the methodology, the end points, so forth, at the end of the clinical evaluation.

And the laboratory people, that's not what they do for a living. So we had to set things up. I talked Jay Siegel into coming out of the laboratories, he's a very good methodologist, and he headed up the clinical review. And so, you know, we needed physicians who also understood clinical trial methodology, and that wasn't CBER's thing. They regulated blood, allergenics, and vaccines. So, you know, it was just creating a whole new thing, and as part of that, because there was much more activity than there was in blood allergenics and vaccines, in therapeutics because everybody, now they could make these monoclonals, they could make these cytokines. And so we had to have good tracking, and we had to have a handle on things, we had to have assistance.

JS: Right. But was there not a division of clinical trial methodology in the office?

JW: That was what Jay Siegel headed up—the clinical group.

JS: Okay. A couple of the things I want to point out during your time in that office, a couple approvals, and from time to time as we talk, there's some others that I'll bring up. But for now, I want to point to a couple. One was the approval of interferon beta B, for multiple sclerosis, or relapsing remitting.

And also Dornase alpha, for cystic fibrosis. These were very unusual, both technologically and therapeutically. And I wondered if you could just say a little bit about those two aspects of those approvals.

JW: Certainly. Well, with the interferon, there was a small molecule treatment that CDER had approved for multiple sclerosis, and probably it worked by inducing interferon. So this was a matter of giving them the interferon directly. A pretty large trial was done in relapsing remitting MS. The trial was done in Canada and the U.S., and they also had CT scans showing that the treated group had fewer brain lesions.

But the neurology community has always, you know, couldn't find a correlation between brain lesions and symptoms. But the trial showed the symptoms, you know, the relapses were diminished. So we took that to an advisory committee at CDER because CBER just had blood and allergenics. And I think they ended up having a biologic response modifiers committee, and this is a biologic response modifier, but that didn't really have very many clinicians on it. So we joined with the neurology committee.

JS: Was it unusual to use advisory committees of other Centers in the Agency?

JW: Yeah, well a little. But in my first introduction to CBER, I think before I'd even gotten on board, but I had been hired, I went to the public meeting and advisory committee for tPA (tissue plasminogen activator), which was kind of a blood bath. The blood people in CBER had taken tPA to the cardio renal advisory committee in CDER. They had agreed upon a certain end point—and these were blood people, they weren't cardiologists. They'd say, "well thrombolysis of the coronary arteries is sufficient to prove this new treatment." And of course the cardio renal committee totally turned that down. They said, you know, "you have to show that you help the heart." Right? It's all about the heart. So that was quite a controversial thing. And I'm sitting there wondering what I'm getting myself into, right, watching this whole thing unfold.

So then I took Betaseron to the neuro, whatever they called it, that advisory committee. And Paul Lieber was a neurologic division director at that time. And he was bitterly opposed to approving the drug based on this trial because he said you need two adequate and well controlled trials. I was bitterly and publicly opposed. He opposed it at the meeting and so forth. You know, it has to be replicated and so forth. That would take probably four years.

And so we went back and the biologics laws are different. They have to be, you know, pure potent and whatever potency. And so, with whoever was Center director at that time, maybe Kathy Zoon, we all just went ahead and approved it. We had two different clusters of sites from that Canadian trial and the U.S. trial. They basically agreed; they were the same trial but done in different countries and they agreed with each other. And we also had the brain lesions that had decreased.

So we went ahead and approved it over the vociferous objections of the Center for Drugs.

JS: Do you know if Carl Peck was there at the time?

JW: Yeah, and I don't remember what he said. I don't remember. He was, of course, very much toward pharmacology and using pharmacologic knowledge that wouldn't have necessarily helped you in this case.

So, anyway, that was that. Dornase was a little less controversial. But it was interesting because of its intention. The mucous plugs that people with cystic fibrosis get are partly composed or held tied together by this DNA of the cells, the cellular infiltrate they get in the lungs. And so it was shown that by inhaling that enzyme you could break those up and then help clear the mucous plugs. And that was about the best we could do in those days for cystic fibrosis.

JS: Right. But it was, I seem to recall from something Commissioner Kessler said at the time, the first approved therapy that was designed to make people breathe.

JW: That's right. It dealt with modifying the disease rather than treating the infections they get and everything with antibiotics. It was actually directed at the disease.

JS: These would both be considered rare diseases, right, in terms of the number of patients?

JW: I don't know. It depends on what your definition is. Multiple sclerosis is pretty common in the temperate regions of the world. Cystic fibrosis is rare. But with both of those it felt very good to be able to help someone. As you know, 30 or 40 years later. I received a

thank you note from a patient. This is an individual who had multiple sclerosis who said that Betaseron changed her life.

Part 1_26 March 2024_240326_001: 00:40:08

JS: It must have been meaningful to get something like that so long after.

JW: There was a lottery and she got a lottery ticket I guess and she got in early into getting Betaseron because at the time they were just learning how to produce these products. A number of the products that were approved early had shortages and couldn't treat everyone. But she got in and she said it changed her life for the better and she's had a very good life. I've heard this from many patients from many different diseases over the years and it is very gratifying.

JS: So it was actually when these approvals came along, as well as just all the experience you had in OTRR, that you were specifically called out by Commissioner David Kessler in 1994 when he chose you to lead the Center for Drug Evaluation and Research. So when that nomination came out, a lot of trade newsletters were writing about this. I don't know if you were quoted accurately or not, but one of these newsletters has you saying something to the effect that this Center, CDER, “isn't broken, is not broken.” Whether that's true or not, I know you probably had some clear ideas about what were priorities for you. You were nominated I want to say January or early in the year and didn't finally get approval from the department until May.

What priorities did you have for the Center when you started there? And is there anything you might want to share about the whole process of going through this? I know

there were probably a number of candidates for the position, but clearly they knew who they wanted.

JW: Well, I think Jane Henney really supported me and I don't know that it was on the basis of my record, or if it was on the basis of my analysis of what I felt the Center for Drugs needed to do. And again, this gets back to my systems orientation. So when I sat down with her and had an interview, I just presented to her what I thought needed to be done. Yes, there were at least five other candidates I think within CDER who were being interviewed and I did not think I would be selected for this position. So I wasn't super anxious about it or anything. I didn't think I would be selected and I don't think anybody else did either. I think that was a big surprise to people.

What I learned after I took over was different than what I thought, although not totally different. The situation was, in my mind, worse than I thought and was considerably worse. And so, you know, I had to put in a great deal of effort for many years to get things straightened out.

JS: What concerned you?

JW: Well, there was no real system of management and I didn't know that when I took over. CBER had a pretty good backbone of management. They had to run their laboratories and this and that and they had competent people. Not that anybody in CDER was incompetent. So, when I took over, well, first of all, I got almost immediately embroiled in this thing about women and, you know, this regulation we were trying to pass, which people opposed that required demographic information in the application, right? And that reg is still on the books and I had to listen to everybody, sort through that and get that done and that got

done. I don't know what the budget of CDER was at the time. I don't remember. But, of course, undoubtedly in the hundreds of millions of dollars. So, of course, the first thing I asked for when I came to CDER, was to give me the budget figures for the previous year. Okay.

First of all, I said to the person I asked to find out about that, they said to that person, why does she want the budget figures? The answer was she's the Center director, but apparently Center directors weren't supposed to ask for that. Then the second answer was, we don't have a budget. We have a big pot of money and we give out money where it's needed. And the Center at that time routinely gave money back to the Agency. They could be relied upon to give money back. And I knew some of the conditions that people were working in, because I'd seen it in the Parklawn building. And these conditions were not good. And then, you know, there are basic fundamental things. So I told the senior staff, we're going to have a planning meeting in the summer. And I swear this is true, okay. One of them looked at me and said, “what's planning?”

Okay, and I'm there. I have a lot of work to do. So it was true. They did have a big pot of money. They didn't have budgets. They couldn't give me spreadsheets. They could tell me payroll, what they'd spent on payroll. But they couldn't forecast the payroll. They couldn't do any of that.

JS: I'm just curious. You mentioned CBER didn't really operate that way.

JW: Right.

JS: We have other Centers. I don't know how they operated. But it's kind of hard to believe because the Agency does have to put forth a budget to the department right?

JW: Well, that budget can be like almost ported from year to year. And then of course the user fee stuff was put on top of that. Now, when I took over, you know, as you said, the user fee program was in full swing. Mac Lumpkin was the head of trying to implement that. Murray Lumpkin, he was Deputy Center Director. He was very gracious when I arrived. And, you know, helped work with me.

But for example, we were going to put in project management. Project management is very similar to what we were discussing before. Which is, you have to have a plan and timelines and deliverables and Gantt charts and so forth. They said—and many of these were senior people—we aren't going to have other people telling us what to do. We don't need any project managers. So it was a struggle. And of course for a long time the project managers at CDER were ill-treated. And I think that continued for a decade or more in some ways. Not treated as a full member of the team. I think it's only when I took over Office of New Drugs which was only a number of years ago that that happened.

JS: But the Center did have managers of applications though, right, that helped guide that process? Not that that's the only thing needed.

JW: No, they didn't. They had divisions that kept track of their inventory, their workload. But they were both disorganized and understaffed. The reason we got the user fee program is the U.S. had such an abysmal records compared to say Europe or other places in reviewing applications. They would pick them up, look at them, and then put them down because other things arose.

And don't forget that was at a time when a tractor trailer would pull up to the Agency and submit the application. It was in paper and it was voluminous, hundreds and hundreds

and hundreds of volumes. And then people would be expected somehow to go through this. And this was the yellow sticky approach where things they wanted to remember they put on yellow sticky.

Many of the older doctors in the Center were still dictating their notes and then they would be typed with carbon paper so that we had copies by secretaries. The reviews would be typed like that. And they were stored in the document room with the file and frequently documentation was lost and then they had no idea what they had told the company to do. For example, you must do this trial. Hopefully the company had a copy of the letter they were sent and could send it back to the Agency.

So no, there were the clinicians who were the division directors, they had some ancillary staff who would help with the administration, but things were not tracked in the way that you would think of tracking. So the generic program had just come out of the generic drug scandal. And during the generic drug scandal a number of congressional staffers had come to the generics program and told them how to run things. And so the generic people believed they had to, in perpetuity, do things exactly like the congressional staff told them to do. They were terrified, so that was a problem because many of these things were not modern, shall we say, not up to speed. I don't want to be pejorative any more than I'm being. The quality people, the chemistry reviewers, were in the divisions. They had different standards, even for the same drug. If it were used, say, in psychiatry and then used in endocrine, they would have different quality standards for the drug.

And I brought Russ Abbott over from CBER as the executive officer to straighten out the administrative side, which had severe problems. Personnel, budget, obviously budget, so forth. I asked him to do a management survey, management study of this problem. And he came back, and I hadn't considered this, but I'm always ready to jump on good ideas. He came back and they said you should consolidate the chemists into a single unit and make

them have common standards. Now I did that, and 20 years later some of the chemists are still mad at me. They were moved out of the divisions. However, that enabled us to have quality standards that we were able to negotiate internationally in ICH (International Council on Harmonization). Because we couldn't say, these are quality standards for psychiatry drugs, and these are quality standards for infectious disease, and so forth.

So that was a very good move. That was one of the early reorganizations that I did. I pulled the chemists out of the divisions, put them into quality or new drug chemistry, and told them they had to try to get uniform quality standards for pharmaceuticals.

JS: And did that work, or did it work soon enough?

JW: It was wonderful. That group has gone on a trajectory. Now we have a single quality program procedure.

JS: Right,

JW: Because generic drugs are copies of new drugs. So they should have the same standards, right? And why wouldn't the same people look at all of them? They're supposed to be the same quality. So before I left for Operation Warp Speed, this was many years later than what I'm talking about here, I did another reorganization, put all the quality people together, pulled them out of generics, pulled them out of everywhere, put them together, and that organization has really done well. That is a credit to the Agency.

JS: I hope to talk a little bit more about OPQ (Office of Pharmaceutical Quality) if we can do that. So you've had your work cut out for you.

JW: Yeah, that's a good way to put it. Every single thing, like correspondence control, there was no policy shop. Jane Axelrad was here at the Agency. She had come over on detail from the Nuclear Regulatory Commission to try to help set up the user fee program, I believe, or help with generics. I don't remember exactly what she was helping with, but I begged her to stay. I talked her into staying. I said, I need you to set up a policy shop. So she asked me, she's a lawyer, and she asked me, well, please don't have me supervise anybody, but of course she had to. Our policy shop at the time was in CDER's Office of Compliance.

JS: Why was it there?

JW: I don't know. I mean, nobody ever explained to me the reason for this. Frances Kelsey's shop was there too, Division of Scientific Investigations, and she was elderly and ill. We won't go into that.

So anyway, there were all these different, you know, there was no real executive, there was no executive secretariat. Now, you know, even in 1994, the goings-on of the Center for Drugs were of great interest to Congress and to the public. You know, the comm shop, there wasn't really a comm shop. I mean, I don't know how they functioned. They didn't function very well. That's why we got the user fee program, basically. But I had to set up all these things. I mean, I think the compliance shop was in bad shape. When I wanted to put, I think it was John Taylor in as head. I forget who it was.

JS: From ORA?

JW: Well, that's where John Taylor, I don't know where he was at the time. He was in Chief Counsel's office, I think. yeah. The personnel people said, you can't put a lawyer as the head of the office of compliance. That's what they told me. Of course, yes, they did. I'm not one to take no for an answer. I said, why the hell not? That's what compliance is about. It's law enforcement, right? But no, you have to get somebody who's a Compliance officer. You guys are idiots.

So I prevailed on that and put whoever, whatever lawyer was. We've had a lawyer head of the office of compliance ever since.

JS: And that's the way it was as far as you knew in the OCs and the other Centers, too?

JW: Yes. It must have been, right? Because usually they get somebody from the field. But it's really law enforcement. It isn't investigations. So that started the improvement of the Office of Compliance. But it took a really long time. CDER's office of compliance was not in very good shape.

So anyway, I'm an optimist. When I started, I don't know, probably Jane or somebody, they had some change management people come in and talk to me, consultants, and they said, "Oh, it takes seven years to change a culture." And I said, "well, I don't have seven years to get this done." But it was a journey. I think it's better to say it's iterative. You take on different things at a time. But the goal was to turn them from whatever they were, which is hard to describe. See, they had a methodologic core, the Clinical Division Directors were very picky and so forth. They were leaders in the field. Bob Temple was a leader in clinical methodology, right? But they didn't pay attention to anything else as far as I could tell. And that was really the problem. This was a multi-hundred million dollar enterprise with national

importance and you just couldn't run it like, you know, just chaos. So, you know, I don't know had I known how dire the situation was if I'd have taken the job.

JS: So, what's interesting is, here you arrive, the Center is two years into PDUFA.

JW: Right.

JS: And you've described, you know, an organization that kind of surprises you it's set up this way while there are all of these requirements that the Center has to be meeting under PDUFA, right?

JW: Right.

JS: As much as you helped CBER, I'm interested in finding out how you set things up so that CDER could better respond to what they needed to in the time that they needed to respond under PDUFA? And, I mean, there's so many things concomitant with that. The influx of staff that's part of the user fees, right? I know that what you've described so far obviously is necessary in order to do that, but there's more, I'm sure, a lot more.

JW: Right. Well, Mac Lumpkin was really helping and he was setting up the program, the managed program for new drug review. My point is this is within a larger ecosystem, all of which had to work for the PDUFA program to work. So, what was done was we had direct hire for physicians, maybe for other people, so we were able to hire people. We brought in project management and set up the algorithm for how you run a review process. First, you look at the application, then you have these meetings, and I changed that later in the late

2000s to make it more efficient, but this was step 1.0—to actually write down what should be done.

Part 1_26 March 2024_240326_001: 01:00:12

Now, even then, I think there were problems. The idea probably originated in the 19th century, maybe, or even earlier, that each reviewer should write this long diatribe, or long monograph, shall we say, about what was in the application. Then all of these would be put together, and then the next person in the management chain, like a statistician, the clinical person, the quality person, their team leader, then would write something.

Then the person above that would write something, and then came together at the very top, and that person would write something and be the decision maker. So this was very inefficient, very siloed, but that was the tradition, so that wasn't changed. What was done was that there were time frames for these things to be completed, and time frames to decide whether you're going to go to an advisory committee, and time frames for this and time frames for that. And the project managers were there to enforce that as well as the management, Mac Lumpkin and many other people. So if people had trouble getting that done, we looked into it. Why are you having trouble? So there was no more of this pick up the application, put it down, pick it up, put it down type of activity.

There was a concerted effort to get the review, all these different pieces done, put together. There was this giant action package that they put together of documents, and then project managers were trained to do all those things, collect all those reviews, those final reviews, assemble them, see what's there, what's missing, is there a label review, when was that done? There's a lot of different things that have to be done.

And I won't even mention things like, at some point we had to start working on look-a-like and sound-a-like trade names and generic names. And we had to get involved in that because there were mix ups. I can't even speak about the myriad number of issues that arose. But the record shows we were able to get all these things done. We hired the people and we got the reviews out in a timely manner. They were understaffed and they were highly disorganized in the past. So we got them organized and we got more people.

JS: And did you get the paper applications replaced electronically or did that take a little while?

JW: Well, let me tell the whole story of that. One of the things I did when I started and they told me, oh this is wonderful, nobody has ever done this before. I went to every division. There weren't that many. And I listened to them. I had them tell me what they did and what their issues were. I went to the statistical division. It was a division at that time. Bob O'Neill ran it. It was presented to me what they did. One of the things they did was they managed the Adverse Event Reporting System, which it wasn't. There wasn't a system. And they told me, well, we get these reports about adverse events and then we send them to this state and they get microfiched and then we send them to this other state and they get tagged with a name like liver failure or whatever. And then come back and they were running their system off microfiche in 1994 or 1995.

So, they said—and David Kessler at this time was out publicly pitching MedWatch--send in your reports. They told me, we have 25,000 reports in boxes that are undealt with in the next room. And I said, well, how can that possibly be? Well, they said we have to send them here and then we have to send them there and they only have a certain capacity. And so I said we are going to build an electronic system and we built FAERS, the FDA Adverse

Event Reporting System, version 1.0, and that was done by a little before 2000. We won an award for that for federal systems, even though it was pretty primitive, right? Because I went to David (Kessler) and I said, you're out with MedWatch and everything. You have to give me $3 million to do this.

JS: Was this a follow-on from the old AERS, the Adverse Event Reporting System?

JW: Well, maybe it was called AERS. There was no system before. It was these microfiche.

JS: Microfiche. Well, at least it didn't take up as much space!

JW: Exactly. Yeah, there was no electronic system before, strictly microfiche. So maybe they called it Adverse Event Reporting System but it wasn't a system. Or maybe this one was AERS. I don't know. I don't remember. I mean, they went through multiple iterations but I built that first one along with it.

JS: The key is this was the first electronic one.

JW: This was the first electronic system, yeah. As far as electronic for the reviews and so forth, we were gradually getting more computers and there was an inflow of money with PDUFA, right? And so I, a couple years into my tenure, I got some people to help me and I went to every division; this is how I do things. And I said, “okay, we're going to have to go to all electronic.” I said, “you're really going to like this in the future because you're going to have an easily accessible record of what you said, what you told companies, the meeting

minutes, all these things." And that's persuasion, right? But then there's always a 1% where additional suasion is necessary. And I said, "you will never disapprove or approve another drug unless you use an electronic signature or an electronic document." So, I think by 2000 we were fully electronic, except they wanted—and this is funny—the project managers had people send in a giant cardboard that had the label pasted on it, okay? And they were still doing this. And I said –

JS: Like a poster?

JW: Yeah, like a poster, but had the label posted on it, pasted to it, okay? I said, why are you doing this? And they said, well, we have to check and make sure that the printed label looks like what we approved. I said, "don't you know they can print this off at the e-pub system and change it the minute after they print this thing for the poster. So, it's useless." But they just didn't want to give this up. They just fought me tooth and nail. But finally we got rid of the poster. Because how are you going to document or store something like that?

JS: I don't know, but I'd love to find one of these just for documentation purposes, for preservation. I'll have to ask around to see if any are still around. That would be great for us to have.

JW: Exactly. Everything involved change management. Getting everybody electronic, and then getting on the issue with electronic submissions to the company was always very difficult, the back and forth. But, of course, if we were going to do things efficiently, we had to do away with paper and these giant paper records. So, we went and people worked on

standards for submitting the data and the application. And that's at a very advanced stage now, which is good.

We negotiated the eCTD, the Common Technical Document, internationally, so that the companies could send the same dossier to everyone. And that happened. And so, gradually, you know, the Center went over to becoming more of a system, a system of organization. We built a communication shop, we built a large policy shop of lawyers, which has kept the Center out of a tremendous amount of trouble. Everybody just thinks about the new drug applications, but no, we get citizen petitions. The Center got all, they were way behind. So I said, "we have to answer, these are the citizens, even if they're food and drug lawyers, right, they represent citizens, and we have to deal with these." If they have concerns, we have to deal with them. So Jane Axelrad worked with her people and they worked on getting that backlog of citizen petitions down. The generic program continued to have problems and it took a long time to really get it under control until we got GDUFA.

JS: We'll talk more about at that in a moment, but this is very helpful. I probably should add that your predecessor Carl Peck had told me in his oral history that when he started he was, well, I'll say chagrined to find how little computer use there was going on in the Center. And this was in the 80s, mid-80s or so. And try as he did to get more computers in the Center, it was a tough sell.

I might be misremembering this, but I think one individual might have been using one as a doorstop or something.

JW: Well, I would say that persuasion is very important. Persuasion is most important in change management, but you gotta have the stick along with the carrot, and I've always employed that.

JS: So, as I've mentioned, we'll be talking about some interesting approvals along the way. What I want to bring up here is one from 1998, and that was the approval of the infamous teratogen, thalidomide, for the inflammatory subcutaneous complication from leprosy. I wondered if you could talk a little bit about this, what your role was in this decision, and any particular pressures the Agency might have faced, either for or against this approval.

And maybe, if there might have been other influences at work that brought this in front of the Agency, too.

JW: Well, it was a straightforward application for E nodosum leprosum, you know, of leprosy; it was effective. I'm not particularly sentimental or emotional, all right? It clearly worked, it clearly was helpful in a condition that, you know, is a really serious disease, leprosy. And getting nodosum leprosum isn't good either as a complication. So there were folks who wanted to get this on the market and they sent in a marketing application. The division director at the time was adamantly opposed to this, the dermatology division director. So that was interesting. Yes, I had quite –

JS: But was this based on the data, the opposition?

JW: Maybe. I mean, this was, I think, a WHO study. How easy is it to study leprosy? And so it was an older study that they brought forward. They had the rights to the information or it was public or whatever. It wasn't totally verifiable. But again, there was a lot of mechanistic understanding that this would be effective as well. I mean, it wasn't wacky or anything like that, right? So, no, I had quite a role.

But again, I typically aligned with Bob Temple and I would typically talk to Mac Lumpkin, Bob Temple, the different people. But I had a role. I went to the advisory committee. We invited and I talked to the thalidomide victims of Canada. There's an association. And they came down. It was very moving. They stood up or came in their wheelchairs or whatever and they said, we've been terribly harmed by this drug but if it's going to help somebody, we do not oppose the approval.

JS: Was this the meeting at NIH at the conference Center or was this something else?

JW: It was an advisory committee meeting. And the Division Director who was not in the script stood up extemporaneously and made a passionate declaration that this shouldn't be approved. But the advisory committee voted to approve it. It was approved and found a very important use in multiple myeloma off-label and led to lenalidomide--

JS: That was later though.

JW: Yes, and other effective drugs for myeloma. So that was the start of something. And I don't know that we ever got any fetal malformations or anything like that. I mean nodosum leprosum is very different than morning sickness or something like that. Yeah, which I don't think people should ever have, you know, should never have been approved probably as a sedative or some powerful drug, you know, in other countries. So that's what happened. The interesting thing is, I forget who was commissioner then, but they made me meet with a delegation from FDA. And those people basically had torches and pitchforks. They were the…

JS: An FDA delegation?

JW: Yes.

JS: Are you talking about those--

JS: Internal, yes. A group of people.

JS: This makes sense. Okay, go ahead.

JW: This was, I think, before the approval but after the Advisory Committee and I met with them and they were like furious and horrified. How could you approve this drug? This is terrible. This is the drug we stand for. This is the worst thing in the world. How could you possibly do this? I, which I have done many times, just stood my ground. These were not rational objections. They were emotional objections. And I figured I just needed to hear them out. I politely heard them out. And they were, you know, they were very angry and upset and, you know, just heard them out and did that, and then we went ahead and approved the drug with protections obviously against.

JS: Right, the S.T.E.P.S. program (System for Thalidomide Education and Prescribing Safety) and –

JW: Yeah.

JS: I have a recollection of being at a meeting, actually Frances Kelsey invited me to join her, but it was a meeting that was led by Mary Pendergast who was one of the Deputy Commissioners.

And I'm not sure, but do you know—I seem to recall that there was a concern that thalidomide was finding its way into buyer's clubs, the HIV patient buyer's clubs, does that make any sense?

JW: It's possible, I mean people were casting around for anything, right? And I don't know what they would use it for though so I don't remember that being a huge issue with thalidomide. What I remember is, for example, of a member of congress who had myeloma, a representative from New York, a woman. She was on thalidomide for quite some time. Before the more advanced derivatives came out people were using it off label quite a bit for people with myeloma.

JS: So obviously well before we approved it for that.

JW: I don't know whether we ever approved it.

JS: Here's another approval decision that came along a couple years later. In 2000 we approved mifepristone for termination of intrauterine pregnancy. We know this drug is of great interest today and actually literally today. It's of great interest, but I just want to focus back on 2000, and again, it sort of pulls out some of the things you were just talking about.

Do you recall much in the way of external pressure on the Agency to move one way or another on this decision? And I would be curious to learn if there were any threats either to

yourself or others on the review division or anyone else in the Agency that you might be aware of that were part of this decision making.

JW: Well, we kept the review people private as much as we could. We kept names off of things. Jane Henney and I were the public face and I remember when the Concerned Women for America asked me publicly what is your address? I gave them the address of the Woodmont building.

I don't recall receiving any credible threats. I got certainly nasty emails and so forth but not credible threats of harm or whatever. To the first question, the administration was quite interested obviously in the approval of mifepristone and David Kessler and Mary Pendergast came to the initial advisory committee where this issue was discussed. So there was a public advisory committee before the application and everything else to discuss this issue. They were very interested in the progress of the review but I wouldn't say there was pressure. Jane Henney was commissioner at the time this approval went through. So she stood up for the science and that meeting the criteria of benefits would outweigh the harms. So I'm sure there was tremendous interest and it's possible that Jane heard, you know, from some outside parties and so forth. And certainly many outside parties there was tremendous polarization around this issue at the time.

Part 1_26 March 2024_240326_001: 01:20:54

We felt our job was simply to evaluate the performance characteristics of the drug, which is what we did. And there was quite a bit of experience from other countries that we were able to apply to this as well, from the trials and so forth. It wasn't like this was an unknown.

So, yeah, I mean, and we tried to keep both the manufacturing facility and its location and the reviewers and all that out of the public record. Jane Axelrad helped with that. It took some declarations or what have you, but we were able to do that. But Jane Henney and I were the public face of this.

JS: And other countries, our counterparts elsewhere had already approved this?

JW: Yeah, the regimen was in pretty wide use around different countries.

JS: A lot going on in 2002. One thing involved, and this was, I guess, in September that the Deputy Commissioner Lester Crawford at the time had announced the transfer of therapeutic biologicals from CBER to CDER. Could you say a little bit about that and how it came about and what impacts it had on both Centers?

JW: Sure. First of all, I have no idea how it came about. I heard second-hand that Lester Crawford had called Kathy Zoon and told her this was going to happen. I had no idea up till then. Not even the slightest clue or inkling that this was going to happen. Lester Crawford, I don't know. He was kind of—he didn't do anything else except say this was going to happen and it was a done deal. I had to go down to CBER. I went down to talk to the people. There were people literally lying on the floor crying in the conference room when I went there. And I'm sure I was persona non grata. But I said, you know, "this decision has been made. I understand. And, you know, I'll work with you and try to do anything possible to make this, you know, as reasonable as possible."

And subsequently I had to do a lot of things. I actually moved out of my office in Woodmont so that the oncology people from the CBER could come and move adjacent to

Rick Pazdur's group, the oncology people in CDER, because they were bitterly opposed to one another. This way they could start merging their enterprise because probably the largest type of investigation that was going on in the CBER world involved oncology drugs.

So I had to move. I moved to this hideous place down across from White Flint for quite a while.

JS: Oh, three White Flint north?

JW: Yes.

JS: But what, I'm sorry to interrupt but why were there differences between the oncology folks in both Centers?

JW: I don't know. It was probably personality driven—I imagine it was personality driven. I had to continue to mediate this. There were all sorts of issues around the resources. Whoever it was then assigned Mac Lumpkin to try and adjudicate how many PDUFA dollars and so forth would move over to CDER, and because I'm like a non-emotional person, I think CDER got the short end of the stick there because CBER was like in an uproar and you know very emotional about this. It was a very emotional time but the move was accomplished and consolidated. It was the right thing to do. Probably, I would say the wrong way to do it but the right thing to do. There was no objective reason why some of these therapeutics were in CDER and others were in CBER, and they were being treated somewhat very differently, actually. So, that was accomplished.

We also had to begin lining up the technical requirements and try to start converging them and so forth and that was somewhat challenging. But it has obviously been achieved

over the years, and I doubt there are people who remember this with bitterness or sadness. There are probably a few.

JS: This was a long time ago.

JW: Yeah, it was a long time ago, but I was surprised. As I said, the chemists after 10 years, 12 years, they were still unhappy. I consolidated them. So, people remember the old days as the best of days.

JS: Well, there was a long time that the chemists were part of the division. It takes sometimes more than 7 years to change a culture, right?

JW: Right, but I feel like people were very angry at me about this and I had absolutely nothing to do with it. I'm a very truthful person and if I had something to do with it I would say so.

JS: Well, that must have been a difficult visit to Building 29.

JW: Yeah, that was very, very stressful.

JS: So, also, I said 2002 was a very busy year, right? There's another initiative going on that you launched in 2002, the Pharmaceutical Good Manufacturing Initiative.

JW: Right.

JS: And of course it plays into something that you've already been talking about to some extent and that's the importance of quality, right?

JW: Right.

JS: So, were there any particular recent developments that had an impact on this? I mean, you always kind of wonder, well, why at this time, albeit long ago, why did it launch then? And there was a steering committee, an Agency-wide steering committee, that I think maybe had a part to do with this. So, was CDER leading this committee?

JW: Yes. Well, obviously pharmaceutical quality goes beyond CDER. The CVM has a pharmaceutical interest, CBER has some aspects of pharmaceutical quality. What launched this really was, there was an individual in the quality organization, Ajaz Hussein and Ajaz had a background in pharmaceutics. He was a, I don't know, PhD, but, I don't know what his actual degree was in. But anyway, he was very learned, and he was quite unhappy.

The pharmaceutical manufacturing industry just did whatever the inspectors told them to do, and they had fallen far behind. I'd like to say, like the potato chips.

JS: Pringles?

JW: Pringles, yeah. They have more uniformity and everything than the pharmaceuticals. And, that's because they had computerized control and processes. And, the pharmaceutical industry didn't even have online sensors, and they weren't even sure that they would be allowed to; this was so appalling to me. But if we step back, when I looked into this, you know, since (W. Edwards) Deming and his work on quality management—and that was a

long time ago—there has been an understanding of how you actually achieve quality robustly, uniformly, and that is you build quality in, and you engage everybody in a quality enterprise.

Now, I will tell you that when I asked some of the large pharmaceutical companies, "what are your quality objectives?" They said, "our quality objective is to pass FDA inspection," and this was a large pharmaceutical company. I just told them, I said, "that's completely pathetic as a quality objective," and it was in a public meeting we were having with them. Well, it is. It's pathetic, because you achieve high quality by having quality objectives by everybody in the firm understanding those quality objectives. Being dedicated to your product is a very high-quality product. It's not reactive—based on doing whatever FDA says we have to do. So, the proximate cause of all this though was that we were seen as blocking online sensors.

JS: How did they read that?

JW: Inspectors hadn't heard of those sensors because the inspectors were off, they were divorced. Many of the inspectors were chemists, and we were hiring people who had molecular biology as a chemist. This is a personnel system with certain assumptions, as I said earlier—like lawyers can't be ahead of an Office of Compliance. So, they were hiring people with no background in pharmaceutics or manufacturing as review chemists. Well, it's fine to get a higher molecular biologist for fermentation, for making a biotech product, but not for making a small molecule, right? They'd have to learn everything from the ground up. So, the idea in industry was that we can't use online sensors. I had people in our Office of Compliance who told me we will never allow real-time release. You know, the sensors monitor everything the whole time, so if it's okay, you can just send it out the door; you don't

have to go and do wet lab testing at the end. You can believe that Pringles don't wait with their Pringles sitting around until they do wet lab testing on their potato chips.

So, Ajaz really thought we had to change this. I agreed with him, and we started an effort of putting online sensors and similar automation into the process. And it actually took a tremendous amount of effort. It took talking the industry into it, getting the sensor industry to build equipment that was fit for purpose for pharmaceuticals, which are much smaller scale than fine chemicals and so forth. I even did a video for the Italian instrument makers about how we're going to bring automation—line sensors and everything—to the pharmaceutical industry, and we need you to help with this because they make a lot of the equipment.

So, that's what kicked it off and then when I really looked into it and with Ajaz's help and others, we, Moheb Nasr and a bunch of other people, we realized that we didn't have a system of pharmaceutical quality. People were writing individual reviews, then other people would write a review over it, and then a review over that. It was very 19th century. So, we started a larger effort about quality, what is quality, what will enable industry to consistently turn out a high-quality product. How do we monitor quality in a post-market period? Because what they were doing was sampling, and they'd go out and take random samples of things and then test them to see if they made the USP requirements for marketed pharmaceuticals.

Well, I said, “what's your statistical validity here” and so forth? They had no answer to that. So, we stopped that program. I hope it's still stopped. We devised statistically valid sampling programs. Cindy Busey did a very nice study, looking at the same product made in India, Europe, and the U.S., and tested it for all kind of characteristics. And what we found is Europe has the tightest conformance specs. Those for the U.S. were a little wider, and India a little wider still, but all of them were within the requirements. And that would have been predictable by me. So, we had to do all these changes.

So, then it came to the point to really talk about quality with the industry, talk about achieving quality—six sigma (an extremely high level of accuracy in manufacturing), whereas the industry was about at three sigma. Yeah, and India was about at two sigma. Then it turned into a whole initiative, and we thought about how to revise our own review processes and post-market. We didn't have an office of surveillance of quality. Compliance was doing that. And those two groups fought with each other. I tried to mediate that forever. So, finally I did that reorganization. I put surveillance—a technical discipline, not a compliance discipline—in the OPQ, and they've been doing a really good job. So, you know, those were stages along the journey of having probably the world's best pharmaceutical quality system in the United States.

JS: Well, you've mentioned in this a couple times international standards. And one of the things I wanted to talk about is something you've obviously been very interested in: FDA's global ties.

JW: Yeah.

JS: Now, in fact, going to the heart of the quality issue, I know it was very important to you that the Agency get membership in PIC/S, the Pharmaceutical Inspection Cooperation Scheme. That was in 2004. And we were admitted in 2011. Why did it take as long to join, and how did having membership in PIC/S push for better pharmaceutical quality?

JW: Yes, well, PICS is an organization that was started in Europe. And the goal was to bring inspectorates together from a European standpoint; for other inspectorates like in Africa and other places to help them develop standards that could be used and procedures and

training and so forth. And, you know, I thought there was no reason. I was Deputy Commissioner when I did that initiative. They just had a very long process since we're the big guy in the U.S. They wanted to give us a hard time. But we eventually passed all their different hoops and got admitted into PIC/S. But it just seemed like we were in ICH and PICS was off on its own.

And since that time, we tried to be moving PIC/S into collaboration with ICH and with ICMRA (International Coalition of Medicines Regulatory Authorities) and to make sure these international organizations aren't at cross purposes with one another because that's very wasteful.

So, yeah, that was part of the quality initiative that we joined PIC/S, that our voice be joined to the other voices. And CDER was trying to have a more modern concept of what quality is and how you achieve quality. The GMPs were originally written around a quality control framework. They are okay now. You're supposed to have the things you would have in a quality system, but they aren't really oriented around quality management—the modern quality management. So, part of the goal with PIC/S is to bring our field organization into this tent, a big tent, moving in the same direction. I don't think that was achieved at the time.

JS: But you were also promoting closer ties with the European Medicines Agency, EMA. And I wonder if you could say a little bit about that and how those closer ties would benefit FDA and patients.

JW: We're still doing that. In fact, before I left I worked with Theresa Mullin and Patrizia Cavazzoni, and of course, all the OPQ folks, toward a goal to eventually have a single quality approval worldwide. This would fix so many different problems.

Right now, if a company wants to innovate in their manufacturing post-market, they have to send a supplement to maybe 150 different regulatory agencies around the world. And they have to wait until the slowest one agrees before they would change their lines or their process. Well, nobody's going to do that, right? So, when we get a shortage in one country, we don't really know if the product in another country actually conforms to our standards because they're different.

So the goal would be that we would get a collaborative together, eventually, a body that we would participate in, that our chemists and reviewers would participate in, and other chemists and reviewers from all different countries. But we have one small committee approve something and then it would be done.

Part 1_26 March 2024_240326_001: 01:40:14

JS: Having to do the old approach doesn't exactly encourage innovation, does it?

JW: No, it's a terrible discouragement of innovation. And as I said, the pharmaceutical industry, the innovator industry, claims they're innovative, but they aren't innovative in manufacturing. Now, regarding part of what we did back in the early 2000s, Novartis gave some money to MIT to do a continuous manufacturing initiative, and we partnered with them. They built a continuous manufacturing operation soup to nuts, raw materials to tablets, in a room maybe the size of a tennis court. I mean, you could do that.

And then, smaller than a tennis court. And then, Novartis had some continuous manufacturing. We were pushing that. And of course, beforehand, people were interpreting the GMP regulations such that at each step you have to test everything and store it in barrels. This is some of the cause of some of the problems that we see with pharmaceutical quality,

the way they're manufactured. Because if you take something, you've mixed it, and then you put it in barrels while you go to the laboratory and you do some chemical tests on it, and then it has to be cleared by quality and signed off on Well, those things may have settled. Then you may be going to the next step with something that isn't the way it should be. Whereas with a continuous procedure, you're monitoring online as it goes, and you can halt something, or better still, you look at the trends and if things are getting off, you can adjust and keep it. That's the modern way of doing things.

So, anyway, we had a continuous manufacturing initiative, and along with this we also had to sell this to the world. Of course, Europe would be the first, because those inspectors would go there first with Novartis, and so forth. So, we have tried, though, to partner with ICH and with every single regulatory Agency closely. And that happened in a pandemic. We all came much closer together.

JS: I'm sure we did. I'm going to pause just for a second.

JS: Okay. We know that drug safety has always been in the spotlight in FDA throughout our history. There were, of course, several years in the early 2000s when I suppose it was even more so in the spotlight, with a number of high-profile withdrawals, concomitant developments that went along with that, including a very public airing of concerns and grievances by a drug safety officer in the Center.

And, of course, there was the 2007 Institute of Medicine report on the future of drug safety. So, recognizing that this is a pretty complicated story, why did drug safety become such a pronounced public and Agency concern at this time in the early 2000s, and what were some of the external pressures we had applied to us by Congress and medical associations and consumer groups, for that matter. And I guess the bottom line is what was the Agency's

response both policy-wise and organizationally to these issues? There's a lot of questions there. And you ca address those as you see fit, of course.

JW: Well, let's start back in, say, 1994. Sidney Wolfe and Public Citizen and a number of the other consumer advocacy groups had kind of made a sport of this because they could make a lot of publicity about drug withdrawals for safety issues. And as I've described, the review process was not where it should be. It wasn't computer aided and getting these thousands of volumes, how can you go through all this stuff and so forth.

So there were a lot of drug withdrawals and even where drugs weren't withdrawn, perhaps new findings would be discovered after approval. So this was, in my mind, an opportunity for different groups to get a lot of publicity. Similar to the behavior we see in Congress sometimes, to blow things up and make a huge big deal about them because there are people, media reports, and concerns and so forth.

The actual technical fact is that drug safety, if you want to define it by the number of withdrawals, had been improving. Now some, some of the advocates sort of cut the data in a certain way. There was a big bolus of approvals right around PDUFA because all these things had been sitting around and then they all got on the market. And of those, some got withdrawn—a fair percentage, which might be 1% or something. Still more than usual. So that fact was made much of, and they tried to connect it with the speed of review. But actually with the building of the Adverse Event Reporting System, we were trying to make it electronic rather than microfiche-based, such that more attention would be focused on the structure of review and how the data were gone through. Documents were created about how to did this, which hadn’t been there before. If you want to measure drug stafety that way, it had been improving over time.

Nevertheless, there were a number of developments that brought a lot of attention, such as the COX-2 inhibitors and the issues with Vioxx and Celebrex, and the issues with the opioids. The Center had actually approved MS Contin in several dosages in the 1980s and early 1990s, morphine sulfate, and we had no problems with that. And so OxyContin was first approved in 1995, as a form of Oxycodone. It was simply approved as a modified dosage release form. I don't think anybody, the people who were involved in that approval, expected any problems that fed into it becoming a cult drug that fed into the opioid crisis.

Then there were a number of other withdrawals during that time that heightened the interest in drug safety. So, what else could be done? People were blaming it on the prescription drug user fee program because the reviews were quicker, but clearly putting something aside and then picking it up again and doing it off and on and taking a long time, that didn't make the drug any safer. Reviewing it in a competent and efficient manner didn't make the drug any more dangerous.

So that was a fallacious assumption, but even David Kessler kind of bought into that and hinted, oh, we're doing it fast and everything, but he knew nothing about the mechanics of a drug review. You know, this was just a sound bite, but it was a sound bite that had a lot of saliency. So what did we do? Well, over time, we formed safety teams in the divisions.

Eventually, I formed the Office of Safety and Epidemiology, a separate office to do post-market surveillance because the other accusation was that the people who had approved the drug were too, you know, committed to its effectiveness and were unwilling to contemplate the idea that it might be dangerous.

The actual fact is, I think, that the people generally in those divisions were specialists. You know, they were dentists or gynecologists or endocrinologists. They understood the disease and the need for treatment and that's why they did the benefit-risk balance differently than somebody who was just looking at the side effects, because this is all a judgment call

about how do the benefits balance against the potential and known harms. So what we did over time is build up not only the monitoring system, but under ICH, we had agreed on a safety database of a certain size and that was the first time and that was in the early 90s. That was the first time that something had really been articulated about how many patients needed to be exposed and for how long before. That used some statistical principles to figure out what kind of side effects you could understand.

Generally, you need many more patients than you would think to find out a rare side effect. Generally, like if it's one in a thousand, you need at least 3,000 people to even have a reasonable chance of finding it.

JS: So would something that affects only one in 20,000 or so, like chloramphenicol, ever be picked up in a normal drug investigation?

JW: No. And that's something that people do not understand, especially if you have all this rhetoric going around about the fast review. or it was about the reviewers who felt like they made a decision and then they don't want it reversed and all these accusations. So yeah, there were many hearings, there were many activities, but generally we tried to improve the system, getting to electronic review and reviewing the safety database. At least with the information that we had, we could analyze electronically, we could analyze it in a regular manner. It had to be submitted electronically to do that.

You know, again, when I took over, people were getting electronic submissions and they were putting them in their desk drawers and so forth. There was no system for accessing and archiving the electronic submissions that were received and reviewed. They were on disks of different kinds. That took a long time, but we had to put all that in place and then eventually we moved over to where people were submitting data sets rather than printed

documents with all these printouts. So gradually you could see the trend that there were fewer and fewer drug withdrawals.

But whether or not the benefit risk calculus ever became more toward benefits, basically, it's just hard to get people to understand what we're doing. For a cancer drug for a cancer with no current treatment, we'll accept a lot of harm, we'll accept fatalities. If overall there's a survival benefit, maybe some people will die from that treatment and yet it is accepted. And that's hard for the general public to process this.

Whereas for a headache drug, we're not going to accept that kind of harm because, there are other alternatives out there and most headaches aren't too bad. So this is much more technical than people think, and determining the harm is harder. But anyway, these accusations were, as you said, by our own staff and others, were about post-marketing. So we set up much better post-marketing systems. We also began to set up Sentinel. That was when I was in the commissioner's office. Rachel Sherman helped me and she came back to the Center with me and we set up Sentinel to have more active surveillance.

Sentinel has turned out to be used for signal work up. We get a signal that somebody says this drug causes X. We can go into Sentinel and see if that's true or not. And that's really helped to quiet things. Because what happened before is, say, with rosiglitazone, people said, oh, it's causing it's causing heart attacks and all this stuff. But then it turned out that probably wasn't the case. But now we can go into these large databases of observational data and figure out more things. And before that becomes a causes célèbres, we can address it publicly and say we looked and we haven't found this, for example. So that's my take on this.

Of course, it's the hook. People don't like the pharmaceutical industry. And there's a whole contingent on the left wing ready to pounce on anything. And they also believe that the Center, because of user fees, is beholden to pharma. I have not seen that dynamic in the staff, period. I haven't seen it. They surely wish that they were funded totally by appropriations, but

they aren't. And there isn't a clear link between their salary and user fees; those go to Treasury and it's appropriated to us, in a sense. And so, they don't see themselves as beholden in any way to the pharmaceutical industry.

JS: How does the staff perceive this, or how does this affect them when there are these accusations of being in bed with industry?

JW: Well, I feel like the staff is often overly conservative about what they do. And I believe some of that is all these accusations all the time. And it's human. So if people are constantly watching you and accusing you of being, too fast, or too aligned with industry, or whatever, then you're going to be extra cautious because you don't want to be one of those people whose name is in the paper. And I feel this disadvantages development programs, not in chronic disease, but more in rare disease and other areas where it's very difficult to study them, and they're not going to do the classic development program. There is always a lot of concern about that from the reviewer staff.

So as I said, I think they would much rather be funded by appropriations, and that might decrease their conservatism a little, but not too much because these accusations, whenever there's a drug withdrawal or a new safety signal, then the accusations come up again.

JS: And these accusations were flying long before PDUFA came along.

JW: Absolutely. Well, and the rate of drug withdrawals was higher then. So I think over time this has settled down quite a bit. Now much of the debate is around accelerated

approvals and the withdrawals there for lack of efficacy, but you don't see as much constant noise as we used to see about direct safety.

JS: I want to talk a little bit about the cross-Center initiatives task force and what came from that. Now, this was a task force that you chaired and their report, "Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products," came out in 2004. If the term regulatory science wasn't known to many people before that, it certainly was after that.

So, number one, why did the Agency issue this report—what led to it? And what were the key points that came out of it and how did this have an impact on the Agency and, perhaps more importantly, on parties outside of the Agency?

JW: Well, it came about when I went up to the commissioner's office to work with Mark McClellan and I left my deputy in charge of CDER and I initiated this report and wrote it. The issue was, of course, that at that time there had been this hope that the pharmaceutical industry could have high-throughput screening, would save everything and get all these drug candidates. That wasn't working and they were in a slump, which was reversed after the human genome project and then all these targeted therapies and better understanding of biology has reversed that to a great extent. But what was clear to me and had been clear for some time was that NIH funds a lot of basic science research, a huge amount. But the development science had been left to the pharmaceutical industry and device industry and so forth, and there were very few grants or any kind of support for all that translational science. There were something like I think 25,000 papers published every year on potential new biomarkers, but they were little case series by academics, and they weren't worth squat as far as actionable data and so forth. So I wanted to make the case that somebody needed to work

on this translational science. I don't like the term regulatory science, but of course we have used it. The term is sort of denigrating in my mind because of the sense out there that it's the basic science that's the hard science, and the basic medical science, not this regulatory stuff. It isn't regulatory science anyway; it is actually evaluative science.

Part 1_26 March 2024_240326_001: 02:00:46

So you have some wonderful new discovery in the lab. How do you tell whether it's worth anything? What you need is to have the science to see whether it's useful, and that science is the same whether you're going to submit it to a regulatory Agency or not, although typically regulators like FDA tend to be more rigorous on what they require. So anyway, I wanted to make that case that people needed to band together and work on developing these translational tools and that has become a term of art now. Those tools are like new toxicology methods, like all the alternative animal alternatives, biomarkers of all different kinds, new imaging agents, and so forth.

What happened with that? Well, the C-Path Institute formed in Tucson. I helped with that. I went out and helped the community, talked to the community, and they put up the money.

JS: And that was Ray Woosley.

JW: Ray Woosley, yes. And NIH had the biomarker consortium at FNIH (Foundation for the National Institutes of Health), and I was one of the founders of that; they brought together people to work on different biomarker projects—I think that was one of the first times that's led to a lot of things. Now they have many public-private partnerships where they do

development work, including much on basic science, but that was a good one. I was sort of executive lead for the OMOP, Observational Medical Outcomes Partnership, which was at FNIH. That was for post-market surveillance. They developed the OMOP data model, which has now been used by OHDSI, which is a huge international organization devoted to observational research.

That's one of the things that needed to be improved too: how do we use real-world data. And so that was an early effort on real-world data that has proven pretty fruitful. So, there were many things on the outside. On the inside, I tried to set up—and it still has been very rocky—the qualification processes. For example, say somebody thinks they have data or they have a new biomarker; how do you prove that it is fit for the purpose intended? And that's what the qualification programs are about. We have them for biomarkers and we have them for patient-reported outcomes and similar things now.

JS: I see. So, clearly people are going to claim to use biomarkers as evidence.

JW: Right.

JS: And we have to agree to that, right?

JW: Right.

JS: There are also a whole range of consortia that followed on from the critical path, right?

JW: Yeah, yeah. Pharmaceutical safety was one area; they submitted some renal biomarkers and that was very good. Those were adopted for early signs of kidney damage because we had very insensitive measures in humans for kidney damage and so forth. So, lots of consortia and efforts were put together. The Europeans had their big set of projects that the European Commission set up, and some of those had to do with biomarkers and translational science of different sorts.

So, I think it was sort of a wake-up call. Here there's a tremendous institutional inertia because there are all these groups out there—universities and the states and all these people dependent on NIH grants flowing. Those grants flow to basic sciences and are given out by the institutes. And so, to move that a little bit, I did talk to NIH and I tried to get them to pay more attention to the clinical grants they were giving out, and I think they have improved their process somewhat. I told them—and it became a term of art—you fund small crappy studies, which was totally true. Those 25,000 biomarker papers, for example, many of those had NIH funding and yet they were non-actionable information.

It was really an effort to try and get a framework to get people to think more broadly. Here we have the basic science in the laboratory, but how does it get to people? NIH has these reminders at Lister Hill on their campus that "we bring health to the public." Well, how do they do that? They bring papers, scientific papers, right? And they do some translational work, but not a whole lot, not a large proportion of that. And some of the clinical work they do is not worthwhile, in my opinion; it isn't worth federal funding.

JS: Well, where's most of the money coming from to support translational work? Is it from industry? NIH is doing some, obviously.

JW: There isn't very much, period. Industry isn't going to fund things, generally. That's why we tried to put these consortia together, because why would one one company fund something that then everybody else gets to use? They spend millions of dollars on developing, say, a biomarker or something, and then everybody gets to use that. They're competitors. So the private industry is not the best place for this type of scientific work. The problem is it was not considered—and still isn't in some quarters—scientific work. And so it's considered derivative, that's why I don't like the term regulatory science, because that suggests it's just something you have to do to get through the regulators. That's not true at all. It's something you have to do to determine whether it's useful.

JS: You've mentioned all of the crappy papers or whatever you called it, but what sort of actual products have we seen come out of this effort to look at drug development in this new way?

JW: Well, I think we've seen these consortia, and they develop regulatory science tools that people can use. Some of them have become very useful. Like I said, for example, the renal safety biomarkers are used. If there's a question about kidney toxicity, often they come in and just discard the drug, rather than put it into humans, because there wasn't a good way to monitor. Now they'll monitor in phase one and see if any of these biomarkers are disturbed. So there are a lot of things like that.

There's a lot of work going on with QTc prolongation, and that's a scientific tool. Right now, they have to do a thorough QT study, but it may well be that they can use the ion channels and determine the drug's effect in vitro on ion channels and not have to expose volunteers to high concentrations of the drug to see if it prolongs the QT interval and so forth. So these are all incremental steps. There's not been some giant explosion, but it really, in

every field people are working on it. Patients are working on videos that can be used in validating patient-reported outcomes, which is probably much better than, say, taking child patient into a clinic and making them do some artificial thing. They can simply video the child doing their ordinary things in their home, where they're more comfortable and see if they're improved or not, and so forth. So both patient advocacy groups, industry consortia, people like C-Path and other consortia are all working on these techniques. They probably would have been anyway, but also there's qualification programs at FDA that they can put their results through and get them used by the Agency. EMA set up one of these too, so they're working with this, too.

JS: I suppose the Agency and EMA communicate frequently about these too, right?

JW: That's right. But with the absence of resources, FDA isn't a funder, and as I said, the industry isn't interested. They participate in consortia because they're competitive. Other people have to contribute too, and so they're not just doing this on their own dime. But where are the departments in clinical medicine or translational science? There used to be something called experimental medicine, and that kind of went away, and so there really aren't departments of clinical trial innovation or clinical trial methodology. There aren't such things. And until very recently, clinical trialists at the big universities, the prestigious universities, they were second-class citizens.

People since the 70s have learned so much about human biology, and biology in general NIH has funded all that, and we've learned about how a cell works and systems in the human genome and to some extent how that works. We haven't learned a lot about how the brain works, but they're working on it. So these were incredible breakthroughs and advances in knowledge, but what it did is put this other knowledge aside, and so nobody

really funds that, and so that's what I meant by stagnation versus innovation. You have this tremendous explosion of knowledge on the biomedical side, but then the evaluative side, how are we going to tell which of these innovations are worthwhile to develop further and pay for, for example?

JS: Well, it just seems to stand to reason if we have a better idea of what evidence-based end points we can apply to our evaluation techniques, then that would be in the best interest of the patients, of the industry, and certainly the Agency, too.

JW: But there's no funder set up for that. So that was the conundrum I was really trying to address when I wrote that.

Part 2a 22 July 2024 240722_002: 00:00:00

JS: Okay. This is July 22nd, 2024. My name is John Swann from the FDA History Office. I'm here with Dr. Janet Woodcock to resume our oral history interview for the series of oral histories of the History Office. We're again in Silver Spring, Maryland on the FDA campus. Dr. Woodcock, thanks so much again for all the time this is taking. I appreciate your sticking with it and look forward to continuing the next part of this oral history. So, we covered much of what was going on in the 1990s and very early 2000s before. I want to move on to your moving around, literally where you've been in the buildings on this campus. In fact, I think you might have started out in the old Parklawn building in Rockville.

JW: I did.

JS: I understand that when the White Oak campus was being developed and opened up, particularly buildings 21 and 22, you moved out there. That might have been around 2005 or so, I think.

JW: Mm-hmm.

JS: And then when Building 51 was completed, around 2008, you moved on the other side of campus there.

JW: Well, to be frank, I think I didn't move. We moved, neutral. I had a swing office here, but also because we had offices all over the place.

JS: At WOC 1 &2? (Woodmont Office Complex buildings 1 and 2)?

JW: Yeah, and so we moved. I didn't want to move the whole front office there because we needed enough space to hold the people who did move. So, we moved them, and we had to do a lot of things. Nobody wanted to move to White Oak. I was the one who raised my hand and said CDER will move. Because they didn't know who would move and we all couldn't decide. I said, we'll move, because we need to be together, because we were scattered all over Montgomery County.

JS: CDER was?

JW: Yeah, generics was up at Gude Drive and so forth. And people were in Parklawn, people were in Woodmont. I actually think I had moved out of Woodmont because the CBER people had moved in. I moved out so that their oncology group could be co-located with our

oncology group, because they were having bitter rivalries and problems and they needed to get their act together. So I moved to White Flint.

JS: Oh, White Flint North?

JW: Yeah, it was a hideous building, but I moved my front office out there and moved it out of Woodmont. But anyway, I told the Agency that CDER would move, and so we planned all kinds of activities. We had picnics out here because you know how people are. They don't like change. Some people lived in Gaithersburg, they would have a bad commute and so forth. So, we stress that there's enough parking, we have a shuttle from the Parklawn building, and all this kind of stuff. But we had picnics and we had parties and we did all this stuff to entice people.

Of course, now that they're here, they wouldn't want to leave this beautiful campus. But, yeah, there were problems because at the time people were still using paper, like in the library and so forth. And, we had to explain to the Office of Operations that we needed the document room with us. So, that's how it got to be built in the basement there. And then we said we were going to need a convening space, but there were a lot of hotel rooms and different hotels and things around here that we could use. So, we got the people to move. And then when they built building 51, that made enough space that I could move a lot of the rest of the people here, and move my front office to 51. So, that's how that worked.

JS: What sort of documents did the Center have in the document room? I know a lot of the new drug applications are off-site.

JW: Well, they had the active files were here because they would use them. Things that were under review, like INDs and NDAs, would be here—they needed to be in close proximity because they were still working off of paper to some extent then. As I said, I had forced everybody, by the end of 2000, to move to electronic, but that was in the industry. We had to do all the industry stuff with ICH and so forth; for example, get the common technical document. There was a huge amount of work, and none of this will be remembered, but we got a common technical document that then could be converted to an electronic format. And then we had to develop an appropriate electronic filing system. At the time the government wasn't really that ready. I mean, the Office of Chief Counsel told us, for example, you have to print everything, like your emails, and sign them. That was not the right answer. But that was the belief at the time. So, we had a rough transition, I think, to electronic.

So we needed a document room here because there were many paper files they still needed to refer to. And there were bitter fights about this, how many files could be here versus off-site, how long would it take to get an off-site file to here if somebody needed it. All this kind of stuff I had to work through. But we finally got here, got our documents here. That doesn't mean CDER was consolidated, because generics was still up at Gude Drive. And that wasn't until we got Generic Drug User Fee Program, and we got the extra buildings over on this side of campus.

JS: Right, the southeast quadrant.

JW: Yeah, we were actually able to move them down. And then when the CBER people moved, the review people had never been on the NIH campus, like the Office of Therapeutics people; most of them had not been, except the lab people. So they had to be moved in and accommodated too.

JS: It was my understanding that some of the design elements in the CDER buildings were considered by you not working in the best interests of the staff and the work they needed to do, and that those designs were changed. I wonder if you could say a bit about what happened there, because I'm sure the staff appreciated your intervention.

JW: Well, some of it was changed, some of it wasn't. I mean, there's a second-floor corridor that goes all around.

JS: You mean all around the campus, right?

JW: Yeah, the bridges are on the second floor, and that was something Jane Henney had seen. I forget which place we went to and toured, but they showed something like that. I got bitter complaints from the staff about the noise and everything, so that wasn't able to be changed, because then you had people walking right in close proximity to their offices, otalking and going to the cafeteria and everything, all this kind of stuff. So yeah, I think we had to change. Buildings 21 and 22 were never designed as nicely as the other buildings.

They had a more bureaucratic office building look to them, but people need a home, they need a place where they know where the divisions in the Center are located? They need that in their hearts. Even if they're hoteling they want to know, for example, where is the division physically. And you have artifacts there, and you have the leadership there, and maybe a little conference room where they can meet. So we had to do those kinds of things. I had read a lot about human-centered design, because I designed my own house a very long time ago. Before I did that I read a lot of books and developed some understanding of what humans need versus what is architecturally attractive, which is a different thing. And so,

those buildings looked nice, but inside they were kind of worn. And so we got these sites where there were central areas, so people could have a home. For example, my division is on the third floor, and even if someone is up on the fifth floor, or wherever, they'll know where my division is, where the leadership is, our conference room is, and our support staff is. So people knew they had a space they belonged to.

JS: As the Center grew, changes had to be made to the way space was apportioned, particularly for your Center, as it was growing faster than any other. And I guess there were a lot of things that must have changed to accommodate that, right?

JW: Yes. We always had more people than we had offices, so we started doubling up and giving people work at home. So we were way ahead of many others on this. My husband worked at NIH, and their policies were very restrictive on working at home. They were very suspicious of it and everything. But we got work at home very early so that people could double up, and they wouldn't both be in the little office at the same time. We negotiated with the union. We had to assign office space based on seniority, including window offices. We'd get our new medical officers and they'd be in an internal shared office. These are people who came from some academic institution, or they'd been in private practice and they'd been the doctor. So, there were some hard feelings there that we had to deal with. But the ability to work at home really depressurized things and enabled people to, for example, not commute so much, which was good. Parking was limited, as you recall—we had all kinds of issues. That's how we got our heads together. We got valet parking we could double-up the parking.

JS: The way NIH does it, I think.

JW: They do, yeah. At that time we had to, even with people working from home. So I spent a lot of time and energy on all these logistical problems that the Center had as it grew, but that's just the way it is. There wasn't much public transportation to the site. The county, in order to encourage use of public transportation, restricted the number of parking spaces that could be built.

Now, I understand that, except there was really no viable public transportation here. People could take a bus from the Silver Spring metro, and they did, and of course there was a shuttle from over at the Parklawn building, and some people came from there, but people live all over the place. And they did commuting pools, all kind of things to try carpooling and incentivize that to try to get people not to park on campus. But it was tough, and those were some of our solutions. With the valet parking you could double park the cars and get quite a few more cars on there.

JS: Were there other Centers that were using the work-at-home approach as extensively as CDER?

JW: I don't know. I tried to keep a low profile because the other Centers weren't as crowded as we were. .

JS: Your position changed in April 2004. You became Deputy Commissioner for Operations and the Chief Operating Officer. So, why did you change positions, and why at that time? Also, what was your role in this new position? You'd been, obviously, CDER Director for about 10 years—you started in 1994.

JW: Ten years, yeah. Well, that was a long time to be doing that, and like I said, there were always problems every day and dealing with problems. Actually, what happened first is Mark McClellan was Commissioner. That was earlier—I don't know exactly when. But I went over on a detail to help him, because he had a lot of ideas about improving drug development and everything. I wasn't going to be able to make that happen and have all these duties I had a CDER Director. So I had my deputy, Steve Galson, run the Center to some extent, although I remained involved. And then I went over and talked to Mark about this. That's when I wrote the Critical Path Initiative, on detail, and we got that report out and made sort of a big deal about it, like we really need to do better at the science of development, which is really what that was about. Then Mark went and became CMS Director, and Lester Crawford came in and asked me to be his deputy. So I was the Deputy Commissioner when he took over. That was a very fraught time. But I tried to get the Agency's budget straightened out, and planning straightened out, and things like that, but it was difficult. Lester was there for a while. I was his deputy, then he had to leave. He left. Then Andy)von Eschenbach) came over. And then the administration brought in this individual John Dyer.

Now, Andy is more of a visionary. He's not much of a manager. So I think the administration wanted to get somebody to run the administrative part, so there I was. I was his deputy, and I was sitting in the office with him, Andy, and then one day his assistant says to me, well, you have to move out before Monday, to some office down the hall, because another deputy's coming in. This guy John Dyer is coming in.

JS: Were you aware that this was going to happen?

JW: No. So, of course, my assistant and I and other people had to move all my stuff out of the office. Andy didn't tell me about this as his assistant did, so we moved. I moved out, and

Dyer came in. He'd been at CMS where he was kind of an administrator or something. In my mind, he was not a positive influence. He was one of those more autocratic managers. He was the one who got the contract for the data Centers, like in Annandale (Virginia) and so forth, over a ten-year period. It might have been worth maybe $100 million—I forget how much it was, but it was a lot.

JS: So, he arranged that when he arrived here?

JW: Yes, he did things like that. He was a contract guy and a big wheeler dealer and everything. But he took over the budget, and so it disappeared into not a planned budget, in my mind. Into whatever he wanted to do with the money, and so I continued to do a lot of other things that I was doing as Deputy, but I really wasn't running operations anymore. He was. So I went back to CDER before the election and took over as CDER Director, because Steve Galson went and became acting Surgeon General.

JS: Before this happened, you were named the Chief Medical Officer of the Agency.

JW: Right. I was doing a lot of things, whatever problems were in front of my Nose. There were a lot of problems, such as a lot of pharmaceutical quality stuff I did at that time. I talked the Agency into joining PIC/S, the Pharmaceutical Inspection Co-operation Scheme. I resolved a lot of issues amongst the Centers, jurisdictional issues, and things like that. That's the kind of Chief Medical Officer work I did. I did a lot of product jurisdiction. I did a lot of trying to straighten out things on that side, but I couldn't run operations anymore, because someone else was doing it. So then that's when I went back to CDER. But I was very busy as the Chief Medical Officer and Deputy Commissioner. I did a lot of things.

JS: One of the things that you were involved in before you moved back to CDER was the formation of the FDA Bioinformatics Board.

Part 2a 22 July 2024 240722_002: 00:20:01

And I guess, essentially, that was something to help modernize drug safety communications between the Agency and stakeholders. But I wondered, could you say a little bit about this board and what led you to stand it up?

JW: Well, this is a long history, okay, that even continued until I left the Agency. Traditionally, each Center had their own IT and built their own IT. This is an extremely expensive problem. And so things like even safety reporting and everything, it was all done differently. And I can't remember all the things, but the Bioinformatics Board tried to get some uniformity within the Agency about how we do many of these things and try to both save money and get to a higher level of technology.

JS: Was there was an external component to this in the way of the Agency's work, not just with drugs, but with all of our medical products?

JW: Yeah, no, I don't remember enough about this, but the problem persisted, until most recently.

JS: Well, we'll get into this probably a little bit more when we get to the ODT. So, when you returned to CDER in 2008 there was certainly plenty on the Center's plate at that time, particularly in the wake of the Food and Drug Administration Amendments Act of 2007,

FDAAA, as we call it. We'll talk about some of that in a moment, but could you say just a bit more about your decision to leave the Office of the Commissioner and return to CDER?

JW: Well, Steve Galson was leaving, and I felt it would be better since I wasn't the Chief Operating Officer any longer. My skillsets on getting people organized were not going to be used, and operations had become a more autocratic style of management. I went back to CDER, which had some pretty dire problems. They had the rosiglitazone issue, and that was a huge fight between the Drug Safety Office and New Drugs. They wouldn't even talk to each other. Even when I was in the room, they sat there pouting at each other and scowling at each other and so forth.

JS: And what was the issue with this drug?

JW: Rosiglitazone is an anti-diabetic drug and there was a belief that it caused heart attacks and so forth. This was promulgated by the Drug Safety Office. Some the concern came from its comparison to pioglitazone, which is a very similar drug in the same class. The new drugs people did not feel this was a proper comparison, and of course it was out of this that led the outside world to have a huge uproar about it. Steve Nissen, who's an external cardiologist, had published a meta-analysis of clinical trials claiming excess of MRIs in there. But, he had not really done it properly because he had included the trial that originated the hypothesis, which already had excess. So even if the rest had a balance, then that would contribute to the act. So, anyway, the new drugs and drug safety groups got in a huge fight about it and I had to resolve that.

There was also an unresolved issue about low molecular weight heparin, and whether we could approve it as a generic or not. I had to resolve that as well. I think there were some other issues, and the major heparin crisis came along as well.

JS: There was much going on in the Center and the Director was on his way to another position.

JW: Well, I had to resolve these things. They had been marinating, so I resolved them. As for rosiglitazone, eventually the advisory committee, after much drama and meetings, said that they didn't think it was any different than any other drug in the class. Pioglitazone had had a trial once, which showed it might have a benefit in mortality. And so then other drugs would look worse, like they were causing harm. If it actually had a benefit, you did a comparison. So who knows? It's really hard to find out the truth. But these drugs have been to some extent subsumed by new agents for type 2 diabetes. Also, I decided that we had adequate scientific evidence to determine whether or not to approve a generic for heparin, and that was done for fractionated heparin.

And the other issue were that people didn't know who was in charge, who was the lead. I spent a year or two saying, who's the lead on this project? There had been a diffusion of leadership that was very unfortunate. That was remedied over a couple years, and we got people to understand who made decisions and what the process was, and so forth. So, yeah, I was very busy, and a little bit resentful when I came back that all these problems had been left, had been thrown into my lap. But I dealt with them and got through it. That was when I brought in some consultants, and we did safety first, safe use, and all these different things. We also tried to work on the culture of collaboration and get people to stop being so

parochial and arguing with each other all the time. We were all working toward the same goals. That's when we got the CDER culture team together.

They were the impetus for the farmer's market. Yeah, they organized that, and OO (Office of Operations) took it over and did it, did a very nice job, but they were the impetus. They were people from all over the organization, and they came up with a whole lot of initiatives to kind of get people together, get them more social, talking together, and so forth. But that was a big effort. I put a lot of time and work into improving the culture at that time.

We said, look, "We're all concerned about safety, not just the safety office. Everybody cares about safety. They're just supposed to do post-market safety, but they're not in charge of all safety." But, of course, there were outside people, left-wing, who don't understand the technology involved in our decision-making, you know, how you do these things. They just thought, oh, the Safety Office should be in charge of everything. But they brought a specific expertise, epidemiologic expertise, to evaluating the post-market signals. The other thing I did when I was Deputy Commissioner, we got Sentinel started. Rachel Sherman and I started that, when I was Deputy Commissioner.

JS: What was Dr. Sherman's position at the time?

JW: She was on detail to me. We brought a bunch of people up, put them together like a SWAT team, and we did a lot of things. Of course, we dissolved that, because John Dyer wasn't interested in things like that, but, yeah, but we got Sentinel started.

JS: Sentinel is a very interesting development. We've already talked about a number of initiatives you were closely involved in, such as making medications available, addressing safety issues beyond just through the label per se, the S.T.E.P.S. program with thalidomide,

and a similar effort when Accutane came out. But some of these also came out in the wake of FDAAA, which provided for the ability to draw upon user fees for them, right?

JW: We were allowed user fees to help build the system, which was very helpful. And that was sort of negotiated as Congress wrote the law. What we did when I was Deputy Commissioner is start getting the idea together and brainstorming about how this would work. The idea was, there's all this health data out there in the medical records and the claims data in particular, which is what we had to start with. And could we utilize that as active surveillance, in other words, instead of waiting for people to file MedWatch reports, writing a paper, and saying this drug is causing this problem. We could look and see.

It turned out that it's not that good for active surveillance, but it's great for what we call signal evaluation, because we get a signal, say this drug is associated with increased MI. But often those are false signals, like rosiglitazone. So what we can do is go into this system and do quick studies. After a huge amount of discussion with the outside world, we came up with a plan to have a data center and a common data model, and then we would pay people to transform their data electronically into that system, but to keep their data.

And then they will run queries and send us the results so we can pool them, because then we don't have a huge data warehouse, we don't have people's health data, we don't have any of that. That's done in the systems that already have the data, so it's a distributed query system. That's what we arrived at, and that's what it has remained. Of course, there were all kind of massive technological issues that had to be addressed to set up these queries. How you normalize the data to a common data model, etc. But anyway, we did all that. We paid a lot of money, we did contracts, we got an academic center to be the data hub, and so forth. But anyway, we have Sentinel, and it’s evolving, of course, and probably needs to change because it was sort of ahead of its time. But it has helped the Agency resolve many drug

safety issues. Are they real, are they not real? And that's wonderful, because before they would marinate, and we'd have headlines, and we'd have "60 Minutes" stories, and they'd all be heat and not light because you need actual information to resolve the issue, not people making a drama out of it.

So, now we can very promptly run evaluations when somebody raises their hand and says this drug has a safety problem. We can run this evaluation very fast and determine, maybe not whether it's real or not, but is it real enough that we can find it. If we can't find it, it couldn't be very common, right? And we could keep watching. But if we don't find it, then we say, look, we looked in this database, that database, we looked in Sentinel, but we don't see it.

So that was the idea. But that's in a nutshell of something that took an enormous amount of work, and Rachel Sherman, and a number of other people worked really hard. We brought it back to CDER. Devices didn't have the unique device identifier, so they couldn't use this, really. And most of the other Centers weren't that interested. CBER came on board, and we ran it out of CDER.

And, you know, we did a lot of other things on drug safety. For example, the OTC pediatric market was a total mess, and we worked with the Institute of Safe Medical Practices and we got them to develop standards, such as dosing—a teaspoon, or whatever. We got them to standardize common directions for children, because people would just use any kind of spoon, and they could really overdose, and some of the directions would be ounces, and they'd be all over the place. We got that fixed and we did a lot of different things, because there are a lot of different kinds of drug safety problems. We worked with Merck and others, and standardized a lot of directions, even on the drug labels. There's a whole group on drug mix-ups in the drug safety office, and they did a whole lot of work on trying to improve the

labels, like, how you give the instructions so that people don't mix things up, and how instructions are given in the hospital, for example.

JS: Is this part of the Safe Use Initiative?

JW: Part of it, yes.

JS: One of the other things that came out of FDAAA was the requirement for REMS, the Risk Evaluation and Mitigation Strategies.

JW: We've been doing all these things all along. We've been working on Sentinel, and we've been working on post-market requirements. We put those forward to the Hill as things that should be inserted into the law; we were doing them already, but let's make them really official in law. And so they directed us to do Sentinel, and though we were already doing something like that, they directed us to do it. It gave a stamp of this being a legal requirement, and the same with some of our other efforts. So the FDA Amendments Act was a great opportunity for us to put in some enhancements on safety. For example, that maybe wouldn't have flown otherwise, or would have been more limited. So we were doing things like this already, but through regulation, or just as a project, not as something in the law. I've done this my whole career—to work with the Hill, and get them to stipulate things. It's always a negotiation with the Hill, of course, they're not just going to take what we tell them.

JS: You talked about a number of safety issues here. One thing you mentioned before is the heparin crisis. The Agency invested so much time in thisI mean, there was so much time that the Agency obviously invested in this, from late 2007 to 2008. And I wonder if you could talk a little bit more about what happened there and the cause. FDA is always under focus, whatever we do, but we did respond with a number of things. We developed crucial screening tests, for example, and we identified the eventual source of the problem, so could you walk us through that a little bit?

JW: First of all, there were reports of people having catastrophic reactions when they got boluses of heparin, particularly when they were undergoing dialysis, because that's the first step in dialysis, they get a bolus of heparin. They would have really bad problems. We had the field, as we usually do, go out and get samples, and they wouldn't give us the samples. Yeah, they were going to test them in their own lab, and I had to literally—it's one of the few times I had to exert my authority and say . . .

JS: What was the justification? Did they say this was of regulatory interest or something, and they had to hold onto it? Why would they not release it?

JW: I don't know. They wanted to do it in their lab, but, you know, they weren't qualified. So they had decided maybe there was chitin in there, which there wasn't, so I got it from them. And within 48 hours of CDER getting it, our Moheb Nasr, who I think was head of New Drug Chemistry at the time, had identified the contaminant. We worked with outside parties, other heparin manufacturers, everything. So what had happened is, heparin at the time—and now—is derived from pig intestine, and the biggest source of pigs is in China, although there are other places that have a lot of pigs. And they were sending the bulk heparin to manufacturers around the world who would make regular heparin or fractionated heparin. So they would give them crude heparin. China had experienced a disease called blue-eared pig virus (porcine reproductive and respiratory syndrome (PRRS), or something like that, which killed a lot of the pigs in China. And so they had a shortage of pig intestines. What I learned, because we had some Chinese scientists come over here, was that apparently there had been low-level contamination in Chinese heparin for a long time. What they did was put this over-sulfated chondroitin sulfate into the heparin. That's an easily found ingredient or easily made ingredient. And the reason was the current USP test at the time for heparin was a functional test, not an identity test, so the functional test relied on an anticoagulation reaction rather than looking at the heparin molecule. And so the heparin,

contaminated with chondroitin sulfate. would pass the functional test, and that's why they used it. People who weren't doing identity testing of their bulk product would just use the functional test. And there were, of course, final manufacturers of heparin in China as well.

Part 2a 22 July 2024 240722_002: 00:40:45

And so what we think happened is that, because of the blue-eared pig disease, to keep their supply going they adulterated it much more heavily with chondroitin, over-sulfated chondroitin. We collaborated with some folks at MIT and we found, most likely, it caused an immune reaction by the kind of molecule it is, causing this immunologic cascade; there was probably a threshold of amount. We published that with them in the New England Journal.

So, first we identified the contaminant, and second, we had put in place stoppage at the borders. Then we identified a test that manufacturers could use, because the problem with heparin is it's an essential medicine, and it's needed for many, many things, so it's not like you can just get something else and use it.

JS: So this test that you required, this was not going to be a functional test.

JW: Yeah, it was an identity test. But it was also for the contaminant, so we were able to quickly identify the contaminant. It turned out then that I held a meeting and brought regulators from all over the world here, as well as the Chinese. We met, I think, in the Doubletree in Rockville. We had a meeting because heparin was contaminated in Europe, and they were not having as many problems. They didn't use bolus heparin and dialysis, they had a different technique, and so they weren't seeing as big of a problem. There were congressional hearings that I had to testify in, multiple ones, where they gave out the New

England Journal article among other things, and it was quite interesting. There were families there of loved ones who had died.

Now, it was difficult to sort out, because people have reactions anyway to dialysis and may get into severe problems when they have dialysis, so it was difficult to know which ones were related, but clearly some were. So, at this meeting, everybody shared what knowledge they had. The Chinese regulators stood up and said we've never had heparin contaminated in China, and this is a new problem and all that stuff. And then later in the day we were discussing how much chondroitin sulfate would cause a problem, because the Europeans ended up allowing trace amount, allowing some contaminants, so that people would still have heparin. The Chinese scientists stood up and said that low levels of over-sulfated chondroitin sulfate are not a problem because it's been in our heparin supply for a long time. And I thought this guy may be assassinated when he goes back.

JS: Wow.

JW: Yeah. So that happened. And the Chinese were pressing us to let their heparin in, that it was okay. It was really wild, the whole thing was quite wild. In the meantime, we opened up a crisis center because heparin is in everything. It's in all the test tubes, a lot of the test tubes that collect your blood. And the question was, would contaminated heparin interfere with the test? It's used in surgery every day, such as heart patients requiring valve work and other procedures, and people with pulmonary embolisms who get heparin to treat the clots.

So we had to figure out every place where heparin was, and then alert those people, and bring them into the crisis center. Meanwhile we're dealing with all the manufacturers. It turns out there were sources, say in Canada, that had a fair amount of pig heparin. So, we got through that—we didn't get into tremendous shortages of heparin, fortunately. And then I

heard from one manufacturer that they actually had known. They said not only did they test their bulks for other animal DNA. They sometimes would get cow or sheep or whatever, it wasn't all pig. And it used to be cow heparin before the bovine spongiform encephalopathy happened. So, there was a lot that came out of this. It was a year of effort to get all this straightened out. To get the supply clean, we made the test a mandatory test and we got USP to change their monograph to an identity test. They probably had a functional test in there too. But you had to put an identity test in, and then test for this contaminant, this over sulfated chondroitin sulfate and so forth. So we got through it, but it was a huge distraction, a huge problem. It was impossible to tell the supply chain because it came from slaughterhouses of pigs, and then there was a supply chain to these intermediaries. Subsequently we got an electronic inventory, which was a huge task. But prior to that, we were supposed to do an inspection in China of this new supplier, which had turned out to have a lot of this contaminated heparin in it. And the reviewer ordered the wrong Chinese site because they looked very much the same, and it was very confusing. Now, with the inventory, we force the manufacturers to send in all their sites in a file and we know what's there. It isn't like it was when that poor person got a lot of grief during the Congressional hearings. But I'm not sure that would have changed the problem, because the central problem was they ran out of raw material in China.

JS: I gather there's not really an effective substitute, an anticoagulant substitute that could be used instead of heparin, right?

JW: That was the problem. And also its ubiquity in so many things.
It's on medical devices, it's in a lot of testing. So we worked very
closely with the device center to see if they were going to screw up

tests because it had this contaminant in it at a high volume, and so forth. So it was quite an episode, but we got through it. We very promptly got it off. I feel like the chemists did a magnificent job, getting a test together so quickly, and posting it, and everything.

JS: You mentioned one name in particular.

JW: Moheb Nasr. He was the lead on figuring the puzzle out, what this was, and he was the head of the chemistry group. He was an analyst, so he came from the St. Louis lab, which he had run.

JS: The FDA's laboratory in St. Louis is actually a CDER lab, right?

JW: Yeah, and that is a really good laboratory. Cindy Busey was running it then, and she did a lot of the NMR work that really nailed down what this contaminant was. So, they all did a fabulous job, pulled together. And our collaborators did a great job; they did an animal model, showing how the immunologic triggers would happen, yeah.

JS: What a story. Moving on to a different kind of story, so FDA as this really helpful chronology on its website that documents a history of plan B and plan B one step. That list of emergency contraceptive approvals begins with the approval of the NDA for prescription use in July of 1999, up to the June 20th, 2013 approval of plan B one step For non-prescription emergency use without age restriction. Now, missing from this chronology is what happened in 2011. I wondered if you could perhaps shed a little light on this, including your role and your reaction at the time that things were going on in 2011? And if you care to, perhaps your

explanation as to why things happened the way they did in 2011?

JW: Well, I mean, I tend to be rather pragmatic about all this stuff, okay? CDER obeys the law, so, there are laws and regulations and so forth and a structure about how claims and attended populations are allowed, are approved. So, with OTC use, it's very clear how we decide that a consumer can diagnose their own condition, and then it's tested whether they can read the instructions and use a product appropriately. And so that's how the OTC works.

It's this condition that the person can know they have, like, I know I have headache, right? I don't know necessarily that I have high cholesterol, or something like that. So, say if you wanted to do high cholesterol, you'd have to make a whole plan, an algorithm, and everything about how the person would know they had high cholesterol, before, and could use a drug appropriately. So the Center had simply followed those steps. And then, what about the target population? So if you're worried that adolescents who've reached sexual maturity won't know that they've had sex, or won't be able to follow the instructions, then you test for that. And you can determine that. That's what social science does.

JS: We have a lot of great social scientists in FDA, don't we?

JW: Right, and I was one of the spear-headers of that, because, of course, even though the doctors don't think you need stuff like that, there are so many behavioral issues around taking drugs, and particularly, of course, around over-the-counter drugs. So anyway, that was adequately tested according to the Agency. And so it was according to the rules that people could use the drug, down to the appropriate age, and people could appropriately diagnose their condition, which is having unprotected sex. Maybe the condom broke, or maybe the

person just had unprotected sex. And the person is within such a time period since then, and could use the product appropriately.

JS: Okay, and you said just analyze this down to the appropriate point, or appropriate age, right?

JW: Yes, that's right.

JS: And what was that appropriate age?

JW: I don’t remember. I mean, those are the kind of things I can't remember, but what I'm saying is, it was appropriate. It was the age that was appropriate from the testing, and so forth. And that isn't too hard to understand. This isn't something that most people don't understand. Unlike maybe, I have hemochromatosis, okay? I had unprotected sex, and I'm a female, that isn't too hard to understand. But there's a huge social overlay to this that persists to this day. And it has to do with parental controls, and social feelings about adolescent sex, and so forth. So, the various people in the chain of command felt very differently about this, shall we say, and couldn't maybe go along with it.

And that's understandable. Then the judicial system worked its thing, and decided you have to go along with the rules, and that is really what was decided at the time. But it is interesting. I mean, I had quite an issue with Plan B back before, when I was working in the Commissioner's office, and I was trying to really make this happen, but in a way that would be acceptable to everybody. And it was a real mess. I had to give, like, an eight-hour deposition in front of all these lawyers because we had a lawsuit over it.

JW: Not this later part. Only during the lawsuit in the beginning, because we did our thing; that's what we found. And now, I think that whatever lawsuit that was later, there was enough documentation. Especially with these socially significant issues, we're careful to have very extensive documentation.

JS: Of course. And FDA takes all of its decisions very seriously.

JW: Absolutely, right.

JS: Whatever they might be. You were a strong supporter of the development of a large molecule version of what we had available for small molecule therapeutics for a long time, and what I'm talking about here is the biosimilar program, to enhance access. I wonder if you could say a bit about the work that you did, because I've read some of your testimony on this, including an interesting response to one of your bits of testimony from one member, I won't get into that. But that is one of the things you helped create—a pathway for biologics analogous to generic drugs.

JW: Right.

JS: And I know there was a bit of a lag between the time a law was passed and our first approval of the first biosimilar, but you were intimately involved in this. I wonder if you could talk about this, because I think this is something that was very important to you for a long time before it actually came to pass.

JW: Let me just say from the big picture, the biosimilar program was really great. It made us really look at the molecule. I'm a chemist. I have a degree in chemistry. That program

really made us look with modern eyes at the molecular structure of biologics that have been improved, like in the 90s, when we didn't have the technology we have today. Some of them had changed a bit over time. For example, the glycosylation structure is very sensitive, like to the medium you use, and all sorts of things like that, and any little changes might change it, and can actually have big changes in the performance of the molecule. So, when we had to approve biosimilars, we were looking at the innovator product with fresh eyes, and wondering how similar was it to the one we approved long ago. But that's a big picture observation. My role started with advocating for this with the Hill, and with different administrations. Some administrations did not support biosimilars.

JS: For what reason?

JW: They were not open with their reasons, but they did not support biosimilars.

JS: I didn't know if you've had any guesses, but that's okay.

JW: Well, probably they were lobbied by the innovator industry, that's what I would imagine, but I can't say for sure. And yeah, so I would have chaperones go when I went down to the Hill, and there were even some shouting matches, where a Republican member, a senator, for example, would be asking for information, and the chaperone would say, she can't tell you, she can't talk to you. And so they would have a shouting match, not me. I'd be sitting there watching this. Like I said, I'm a calm individual. It doesn't bother, they can do their thing, and they did their thing. It was annoying, though, because you couldn't get full information to the members that wanted it.

But I not only visited many members, personally, along with my chaperones, obviously, but testified many times at hearings, gave talks about it. We did as much preparation as we could. What always made me laugh is we were criticized that the FDA doesn't have a biosimilars program, and Europe has approved all these biosimilars. Well, we didn't have the legal authority to do it, so that would have been really interesting if we did it without legal authority. So, anyway, there was much, much debate and everything, and I was involved in the drafting and other things. Oh yeah, that usually happens. Most people on the Hill are cooperative; they want to make sure things are technically correct. They will share the drafts and ask for input through channels or not through channels, depending on what the channels are like.

Part 2a 22 July 2024 240722_002: 01:00:52

JS: So, the people who are writing the laws look to the Agency for expertise in shaping that law.

JW: Absolutely, yeah. And they ask for TA (technical assistance), or they may just call you up and ask you, and you have to decide whether you're going to do that or not. I'm not a lawyer, obviously, and I've never been that good at drafting things, okay, but I had a lot of people who would help me and work on content to make it legally correct, technically correct, and so forth. But I was often sort of the conduit for all that.

So, we got that done, but then we had a huge struggle. I'll never forget a very simple molecule, G-CSF (granulocyte colony-stimulating factor), which makes your white blood cells go up—some of them. And you need that, say, after chemotherapy or something to fight off infection. And I met with the division that regulated that, and they told me very seriously

that we need two adequate and well-controlled comparative trials. This was a product that wasn't, like, costly. It was quite simple, had a very good biomarker--whether the granulocytes went up or not. And I just said, no, that's not what's going to happen. But, so the Agency clinicians were really hard. It was cultural, as they had not been involved in generics; the Generics Office did the generics. All they knew was two adequate and well-controlled trials as the standards for new drugs. A lot of them were not big picture thinkers, shall we say, and so with every single division we had to have this fight. They had to be involved because we had to do a clinical trial for most of these. They needed to have a clinical trial, unlike generics, where we just did bioavailability and then the chemical structure. So, the clinicians had to be involved, and the trials all had to be properly designed. You had to decide what the outcome measures were, so it was a huge struggle internally.

Now, externally, even before this started, we had been involved. I was very involved with the rheumatologists because I was trained in rheumatology. I think Rick Pazdur and others talked to the oncologists who would use the G-CSF and some of the other agents, about what the biosimilars program would be and what it would look like, why it would be good, why it would be safe, and why it would eventually lower costs and everything. So, we had a huge fight externally, too. It was a huge uphill battle, because clinicians on the outside, too, while they were happy to use generics, usually, oh, these biologics. They were probably being lobbied by the innovators, who said, oh, it's not going to be as good, and so forth. We used to see that with generics a lot. And so, even the innovator firms with the small molecules would make their own generic line, when their patent expired, and they'd sell a generic, as well as selling their brand, because some people would still only use a brand even though it costs like a whole lot more. And then they would have a generic version of the small molecule, of their own small molecule. Came off the same line, just had a different label.

JS: And they're very successful at that.

JW: Exactly. So they would get both markets—the people who accepted the generics and the people who were sticking with the brand. But they were lobbying, and what has happened is a lot of biosimilar manufacturers, I mean a lot of innovator biologic manufacturers, have made generics of competitors, so they've made biosimilars of competitors' molecules and then they can market those.

But anyway, it was a long struggle with many talks, articles, and personal appearances. And gradually the literature from Europe but also in the U.S. reported that these were just as good, they worked just as well, they're interchangeable, and so on. It was a long time to acceptance, and it was a long time to the first one to come on. That was because Congress stipulated, which was very reasonable, that the biosimilar had to be similar to a U.S.-approved product. Well, in Europe they'd use the European products and they aren't totally the same, so they couldn't use that information to get on. They had to do new trials or new comparisons to get on the U.S.market. So anyway, it all worked out in the end. It just took longer than people thought. But now you have to get a fair number of these products on the market to lower the price, to have competition and lower the cost significantly. So that still has yet to evolve.

JS: But we have a number of biosimilars on the market now.

JW: A large number of biosimilars, yeah. And the Center's moving more and more. Like with insulin, they said you don't have, for interchange, you don't need to show anything for interchangeability. We'll accept them as interchangeable. And the more that they're

interchangeable, the less marketing will be needed, and so that'll lower the cost quite a bit for the manufacturer and maybe they can lower the price.

JS: So I guess it's fair to say there were some issues faced with biosimilars that their predecessors possibly faced when it came to acceptability of generic drugs, right?

JW: Well, not even the predecessors. I did a lot of work on that when I first took over in CDER, because, don't forget, they'd just come off the generic drug scandal. And a lot of clinicians didn't accept generic drugs, and we had to do a lot of work, especially on the quality of the generic drugs, which we're still working on. But we also did a lot of outreach to clinicians, you know?

JS: Okay. So, I want to go back to the 2012 FDASIA, the Food and Drug Administration Safety and Innovation Act. And I'm glad we have a way to pronounce these things without having to say that every time. That provided for, among other things, a new approval pathway for certain drugs, the breakthrough therapy designation. I wondered if you could say a bit about how this new pathway came to be part of the law, and what it added to the whole variety of expedited approval pathways we already had. And I know you have been very closely involved in this approach from the 80s or 90s forward, so this is something that's, I think, baked into your DNA. But the breakthrough therapy in particular was an interesting one, right?

JW: Yes. I think it isn't that it changed the standards for approval at all, but what it did is change the amount of attention that the Agency would put. It also provided through that designation a prominent signal to the outside world that they'll get more money to rapidly

evaluate. It would also get more attention from the Agency to move the product along. This came from, say, Gleevec, which was approved around 2000 and it was a total game changer. It was really, really effective for a disease that caused a lot of problems, like cancers, and so it was a total game changer for a disease. It showed that we ought to really put more emphasis on getting that to patients faster, but how to do that? That was about the time I had met, I think I told you previously, with the cancer division, I think in 2000 or so, and Rick Pazdur wasn't there for some reason. But I met with them and said, look, it's targeted therapies that are coming like Gleevec, and we need to get ready and have our standards and our thinking organized about this. It's going to be different than poison cancer therapies of the past. Gleevec is targeted to the problem. And they said, no, we don't see any in the pipeline. We don't see that. But that was in those five years, since 2000, that was when the targeted therapies really came to maturity, okay, and the human genome had been sequenced. People were being able to understand the molecular basis of different cancers. Turns out that every single cancer, most of them described by morphology, actually can be genetically very variable and different, and that mutation's driving it. And so that would call for a different targeted therapy. And you might have the same mutation in different morphologic cancers, and so you could target several different cancers by their sharing the same mutation.

So, when that coming of age happened, of targeted therapies, we started seeing dramatic improvements in treating a subset of a cancer with a targeted therapy that you'd never seen before, because you were poisoning people before, and hoping the poison poisoned the cancer faster, because it was multiplying faster, right? And hopefully it didn't poison the rest of the multiplying parts of the body, like the bone marrow, gut, and so forth. Too bad, right, so it was this trade-off. Whereas here you're targeting an aberrant pathway and trying to shut it down. So these really did require probably some special treatment when you had people out there dying right now, when this therapy that was in development could

help them and maybe extend their life for a long time, and so should we really wait 10 years and have a traditional development pathway? I mean, that was the question.

JS: Well, we did have other pathways at the time, though.

JW: Right.

JS: And what would those have been, contrasting the breakthrough with the other ones that we had.

JW: We had fast track, and that had been mandated by Congress. It was simply a designation for almost a lot of things. It didn't require evidence, clinical evidence, that it was great or better. It just was a promise of therapy addressing a serious disease, so you can see a lot of things get fast track designation. That gives them certain things, alright. And then we have priority review, and priority review is when everything is done, and the clinical development program is done. And then say we'll review it faster.

JS: Once the data comes in to us, right?

JW: Yeah. And with fast track, if you got to that point you could maybe do a rolling review, and so send things in earlier and so forth. But really what breakthrough is about is, say, you have early clinical data, and you might even get that in phase one in cancer, because you target the therapy, you have people that have cancer in phase one, and then they have a dramatic response. So the question is, what should you do then? Should you do a seven-year

development program when you have something that's clearly better than anything, potentially, that's come before, for a fatal disease?

So the idea was, where we see that, we design a fast track, and we give it a lot of attention. And we devise a program that's shorter, because if you truly have that kind of game-changing effect, you don't need to do all this stuff, okay, because you will have an overwhelming advantage in your phase two trials. So, that was the thought, and we talked. The cancer community was very unhappy with the progress. They were mad at FDA, but it really wasn't FDA's fault. There weren't the products in the 90s, and those we had were all like toxic cancer therapies. They weren't very good, and they were just like riffs on what existed before, and so forth, so this was game-changing.

And we were beginning to see that happening in other disease areas, like rheumatology. So we talked to people like the Friends of Cancer Research, who helped with this, and a number of people in the cancer community in general, advocacy groups, and devised a designation program that we felt would single out these therapies at an early clinical stage. That's different than fast track—an early clinical result had shown a game-changing effect, and therefore merited a shorter development program. Now, if the development program showed they didn't have that effect, then we would rescind the designation, and they would go on like any other ordinary drug. And that's what has happened, because not everything that has a spectacular effect in phase one maintains itself further. Or phase one or phase two. So we got that through Congress and started implementing a program. It turns out, like with the genetic revolution, and the biologics revolution, there were a lot more therapies that were game-changing than you might think, or potentially game-changing. You don't see that very much, say, in infectious disease. You don't see it in a lot of cardiovascular disease, right? We haven't had a lot of breakthroughs, but there are a lot, but in rare diseases, I mean, you have some rare diseases that are so

terrible, you can't even imagine how terrible they are. And we've had breakthroughs there, breakthrough designations.

We've had breakthrough designations in rheumatology. We've had breakthrough designation in dermatology, and you think, oh, dermatology, well they have some of the worst diseases you can imagine. And where maybe you don't die right away, but you live a life of misery for 10 or 15 years; terrible diseases. So, that is what happened. Now, I think the staff at FDA say, "Oh we don't treat these any differently, we don't see any difference," but studies have been done and published that say, yeah, it makes a difference. This designation gets them to the patients faster, most likely.

JS: So this can start as early as signals from phase one.

JW: Yeah, it can, and has. It depends on the disease and how fast the treatment works. Like cancer, you treat 20 people and you start with people who have the disease, you don't do normal volunteers in phase one. And often, in cancer, they start with people who've exhausted other therapies, right, because why would you expose somebody with cancer to an experimental drug that may not work if there's a treatment? So they take people who've gone through all the treatments. And so when you take those people who don't have any other approved treatments, and you treat them, and 10, 15, 20 percent of them have a complete response, that's because nobody has ever had a complete response before, because they've been through every treatment. So, we really need to get this to the people who've exhausted other therapies. And then we'll test it in people earlier to see how it works against the existing therapies. So that's the paradigm.

JS: That same legislation that prompted this, also provided for user fees to support the Agency's generic drug application. So, I wondered if you could discuss that situation: everything the Center had to deal with prior to passage of the GDUFA—the Generic Drug User Fee Amendment—in terms of application backlog, the sort of infrastructural changes that needed to be made, and how things turned out ?

Part 2a 22 July 2024 240722_002: 01:19:44

JW: Well, we had gone through several cycles of PDUFA trying to get a generic drug user fee program in place. In the industry, the first cycle, I think the industry had split and was in two opposing trade organizations, and that persisted through the next cycle, and so we couldn't get anything. But we had to for the generic program, because CDER's budget is very constrained by the user fee programs, because there is a base, an appropriative base, that has to be put against those programs, and it has to be maintained. So the CDER Director doesn't have a lot of ability to shift money around.

And actually, I had to give tutorials on this, to both the generic drug people and then later the OTC people, because they couldn't understand why you can't give more money to OTC. Just give more appropriated money. Well, that’s tied up in the thresholds that are required for biosimilars, the PDUFA program, then generics, so forth and so on. So, a generic industry, of course, doesn't have a very large profit margin, so they watch their pennies very carefully.

But in that third cycle they were under single trade organization, and we had to have a very long negotiation. I personally met and we had dinners with the board of directors of that organization to talk to them. But the reality was, I think there was a thousand generic applications in the backlog. The program was just too small, and it wasn't the right program.

They didn't have a policy office, and believe me, generic drug policy is very complicated. They also didn't respond very well to queries. And the generic industry needs a lot of hand-holding because it's all around the world and everything, but they didn't have time. I mean, they were just swamped with everything. I very personally went through their computer system and it was just home-grown tracking, so they didn't really have that. And so forth. But we finally got it. After much negotiation and effort, we got a generic drug user fee program passed with the agreement of the industry, but they had very tight stipulations. They wanted us to get rid of the backlog by the end of the five-year period, and also be up to date on current applications. And we had timelines. There are also responses to written requests that we had to get back to them on.

So, what happened is quite a saga. The people at the end of this had change fatigue. There was so much change. So we moved the program here because it was going to be much larger, and we did a huge reorganization—we made it a super office. We took away the chemists from the generic program, and that's the majority of the review, and we put them with new drug chemistry, forming the Office of Pharmaceutical Science. Why did I do that? This is very unpopular. I did it because here we stipulate what a new drug is like and we do all the CMC (Chemistry, Manufacturing, and Controls) review. Then we have a generic, and we had the generic chemists guessing what were the problems, what are the issues with this molecule, and how is it controlled? Well, it could be the same people looking at it. Some of them stay here for a long time. So why would you have two separate groups with different standards, when they're supposed to be the same these products?

So, we did a massive change effort along with this, because we were merging new drug chemistry and the generics. And this gets back to what I said about heparin and getting confused about what the site was, we set up the Office of Surveillance within the Office of Pharmaceutical Science, and its job was to figure out what is our inventory of plants around

the world that make CDER-regulated products, and what do they make at any given time. That was a huge effort, because our IT people at the time said we have to do a catch, tag, and release program. We have to pull all the names of these sites out of all this mess. They were kept in something like logs, and they were kept in generics, kept over here and over there. We had to put all that together, create an inventory. And I was the person who told them, you have to do this, and you have to work with the IT people. You have to create an inventory, and they did that, and the upshot of that is we discovered firms that hadn't been inspected ever, like in China, OTC firms. And they developed an algorithm, risk ranking; a firm that had never been inspected was at the top of the list. That took a long time, to work through that list and get a regular road where the highest risk firms were going to be each year, because we didn't have the inspectional resources, and they still don't have them.

Anyway, that was one thing we did. We formed this Office of Surveillance, and their job was to maintain this inventory and then manage the inspections, the surveillance inspections with the field, and they did that. That was a new concept. Then we had to get them a new computer system, to run the reviews on. And the Office of Pharmaceutical Science had to share that with the new Office of Generic Drugs. Then we formed an Office of Policy in the Office of Generic Drugs. I hired Keith Flanagan and he headed the Office of Policy. Cook Uhl was head of the Office of Generic Drugs, and she just gave it her all. It was wonderful. Then we set up project management. They really didn't have that, and that obviously is needed, with a thousand applications and a backlog you have to get through and everything. We did projections of how many we had to do for each time to get this down and get it all done.

JS: Just so I know, what's the impact, if the Center hadn't met the requirement under the law, to clear out a thousand applications and backlog within the five years?

JW: I think the industry would have bailed on the program. I think that's what would have happened. They wouldn't have supported the program because they were very reluctant even the next time. They don't have a lot of money. They don't want to give money, but they actually agreed to enhancements the next time. So, bottom line is, between the new computer system, a massive reorganization with a lot of change management, putting in a new policy shop, putting in new project management activities, and getting all this work, getting through all these applications, we got it done. We got it done, but the people were exhausted.

JS: Well, this also entailed bringing on a lot of people too, right?

JW: Oh yeah, and we had to do all that hiring. Now, we got some special hiring exceptions and we were able to hire people rather rapidly, but they had to be trained, and the Office of Pharmaceutical Science had to do a lot of that because they were hiring all the chemists. But that was the right thing to do, to put all chemistry together. Say, when we had the nitrosamine problem much later, they were all dealing with it, rather than having generics deal with it and new drug chemistry deal with it. Andre Law, who's one of the chemists, started something called KASA, Knowledge-Aided Assessment and Structured Application System. It was the way to submit a structured assessment and then have a computerized evaluation that the reviewer goes through, and then that auto-generates a letter, and then they check it. So, stop writing all these monographs, you don't need to rewrite the story. That's something I've failed to do, and like in much of CDER, the challenge is to get them to stop acting like it's still 1980. But anyway, KASA was successful, and so they can roll through these, and then they have a record of everything. It's electronic and structured and so forth. So I'm very happy about that. But yeah, it was a huge effort. But it not only was successful,

but we also were able to renegotiate the program for another five years at that time, which was very iffy at the time.

JS: But you had managed to get through the backlog.

JW: Oh my god, yes. Yeah, we burned out a lot of people; it was a huge effort. You see, I have a lot of energy, so I can deal with all this stuff.

JS: Well, but of all the things we've talked about, when I started to bring this up I saw this look on your face that I hadn't seen with too many other things we've discussed.

JW: Yeah, we did a lot of cultural work that was really helpful, I think, in getting people to think in new ways.

JS: So it's interesting you bring that up, because that really applies to so much of what you've been involved in, from the beginning until the time you left—getting engagement from the people who are affected by these very necessary changes that can make life very difficult for people, but they're important. Where does it come from? How do you decide the level in which to get engagement? We'll talk more about the last reorg you were involved in later, but this is something that you obviously think is very important for success.

JW: I think the literature and experience shows that top-down reorganizations mostly fail, and the reason they fail is people think this will pass, that this is just another scheme, the whole bit. Why? Because when you look at change, the first thing people think of when you mention a change is, I'm going to lose my job. That's the very first thing they think. Then they

might think this is going to be a real pain in the behind. And then they think, we're going to sacrifice all the good things that we do and go to something bad. So, people generally have negative thoughts, except the early adopters, because they've already assessed that there's problems, and they're more eager to deal with the problems.

But most people, the first thing they're thinking is, this is going to change my job, I could lose my job, I'll lose my authority with my expertise. They think all those things. So, if you come along and have an authoritarian who says we're going to do this and that's the end of it, people will have to comply and be shuffled into new roles and so forth. But they won't understand it, they'll be resentful, and they won't put their heart into it. There have been large numbers of studies, like in the Harvard Business Review, of government reorgs or private reorgs, and unless you get engagement of the people, they are not very successful in their intended outcomes. So, here it's even more salient.

The people at FDA are so tied to the mission, they're totally committed to the mission of the Agency, and often, in their minds, the mission of the Agency is what they're doing right now, the way they're doing it. And so, when you bring up change, you're also threatening this mission in their mind, and so you really have to explain why, why, why, why, why this will make us do the mission better, because why would I do a change unless I would think it'll make things better? I don't do it.

It's a pain in the behind, so I don't do change because I feel like it. I do it because so much change is needed all the time. Because the world is changing, and people and organizations must change too. So, my belief is that that's the core of a successful change, getting allegiance, getting engagement, and then belief in the change, and that will drive the change. And so that's what I have always tried to do, generally, and you know I moved out of my office in Woodmont into a dump over in White Flint, so that the oncology people could start working together, because it had to be done. I mean, it's really important. I couldn't just

tell them get together and work together, because they weren't going to do that. They hated each other. So, you have to do what needs to be done, and the level of my engagement, which I think you're asking about, depends on how deep these animosities go, or resistance to change, or whatever you want to call it. For example, in the rosiglitazone, I was totally hands-on, because those people were fighting with each other and behaving poorly, and it needed to get fixed.

JS: So you learned to assess the situation pretty quickly to see what kind of involvement you would need to have. Do individuals affected by the change normally, or often, expect to have input into the solution?

JW: Well, they should, that helps them. It's a cognitive thing. First, people have to accept there's a problem. When I did these reorgs, all of them, I did listening sessions with the staff, and I talked to them about their perceptions—what's working, what's not working, and so forth. So, I really understood how, at the ground level, people were experiencing the program. Then, when you do that, you also find the people, as I said earlier, the people who have assessed it, who have the big picture, who understand their problems, and who are more or less aligned with finding solutions. Then, you bring in the early adopters, you talk to them about what the change should be, and try to figure it out. Then, once you have a proposal, you go talk to everybody else. You don't want to just talk to everybody else about, broadly, what they think we should do. That that makes you sound clueless. Talk to them about what their perception is of the current situation. That lets them know you're listening, which is what you're doing. But you don't go and just ask them, what should we do? What you do, though, is find the people who have a really good idea what should be done and you enlist them, because they're going to know much more about the program and its details than you do.

Then you can have those people help in crafting a proposal that then you take out again. So, you take a proposal to the broad scheme of people, and that has to identify what the problem is, why we want a solution to this problem, and then what are we proposing. And then solicit input. People can understand that. They might not agree there's a problem, though, because a lot of people just don't have the big picture. They're just doing the daily work and don't see a problem.

JS: And it's easy perhaps to doubt how genuine this effort really is, to solicit what they feel needs attention.

JW: Right. There's still going to be 10, 20 percent, and depending on the organization here, there's what I call a lot of what I'll call sentimentality. Maybe that's pejorative, but people can be just emotionally connected to the way they're doing things now, the history. They're sentimentally attached, not to the actual mission, accomplishing the actual mission, but to the history of how the mission has been accomplished.

JS: Right. Well, we develop a culture here in FDA, especially for those people that have been around for 20, 30, 40 years, and it becomes better or worse.

JW: You know, that's what's so strange about me. I think I've always been an outsider.

Part 2b 22 July 2024 240722 003: 00:00:00

JS: So after about two years of planning and approval, you launched the Office of Pharmaceutical Quality in January of 2015. Could say just a little bit about why this office

was created and to what extent new functions were set up as part of this, and which existing functions were transferred into it? And maybe if you could share an example or two of how this office counseled other CDER offices on quality assessments of drugs, because I know that was part of what you had in mind with this.

JW: That is what I was talking about with the generics because that was actually part of the big generic reorganization to put the generic chemists and the new drug chemists and all together. The only people who didn't move were the monograph people, the OTC monographs, because that was a joint activity which we fortunately got rid of later. But the goal there was to really have drug quality in one place. Quality of drugs that serve the American public should be uniform. And it shouldn't matter if they're generic or a new drug or a biologic or whatever. They should have a uniform high level of quality.

We approve them, we look at them very carefully. We can't just let them out and have them out there. The Agency, CDER, gets thousands of manufacturing supplements every year, and these are industry petitioning us to make changes in, say, how they manufacture something, or specifications, or something like that. And those have to be reviewed and approved by the Agency or allowed to go ahead, depending on what kind of supplement they are. So, again, this was a huge burden on the Agency and on the generics program in centralizing this and making sure we're having the same policies and standards across all drugs. That was the goal here.

And also why have separate programs, because then they would diverge and that's just how life is. So we made them into a single program and we also set up the surveillance function and some other functions, a policy function, that would help them write guidances and so forth in their international negotiations that they needed to do. Because we also started—and Theresa Mullin now is running this at CDER—a goal to have a single quality

approval worldwide. Why should we have slightly different standards for Europe, the United States, Liberia, Japan? Because what happens then is if they want to make any change or innovation to their manufacturing, they have to send a change supplement to maybe 50, 100 different countries, depending on how many approvals they have. And they have to either run two lines or wait until the slowest country approves that before they can make the change.

And this is a huge bar on innovation and manufacturing. They've already started the pilot EMA and it's voluntary, and CDER did a manufacturing supplement together. And they issue separate letters, retained national sovereignty and everything, but it's the same letter. So the goal is to bring more and more regulators into this over time so that the product then that is on the market in all these countries, except for the label, is the same product. So we don't have all these problems with shifting products.

JS: But are there variations in standards of what constitutes quality from legal system to legal system across the nations?

JW: No. In fact, that's a technical issue. Over the years, starting back in 1990 or something, before I even started in CDER and then when I started in CDER, we've driven international harmonization through ICH. And so there's a whole quality series in ICH of what the standards are. We could never have done that unless I put all these quality people together. So we had one quality voice in CDER eventually. But, yeah, it's all harmonized; it’s more or less harmonized internationally. But, you know, they do little tweaks depending on the individual reviewers. But those products aren't any different. These aren't things that matter.

And we could have a single approval because these are very technical things. They're not big things that you put in a statute or something like that. And to the industry, that means

they have to have all these people, file all these separate supplements to a hundred different regulators, and then they have to wait and keep track of which ones have approved it. And they can't change their line so the manufacturing people are stuck until they get those approvals, or they have to set up a separate line for the new product.

It's a huge waste of time, and then we have a hundred different regulators reviewing the same manufacturing change. So the goal is that we get everybody, all the regulators, to join a consortium, and then one team reviews.

Now, we know what international negotiations are like. We have to go a long way to build trust and common understanding and everything to get there. But that's the overlying goal, and there's no reason we shouldn't get there. And that'll help the smaller countries, too, because they can't afford to have a huge staff of chemists reviewing a flood of supplements and everything. But they can contribute one person to this team, and that would be enough. So Theresa's pushing that, and Patrizia's obviously very supportive, and I think that'll go forward.

JS: There's another area of major organizational change that I wanted to ask you about. Around 2018, you started to look into how the Office of New Drugs could be modernized. And I think this included the organization of how the therapeutic review divisions would fall out, and certainly more focus on more drug-specific guidelines. I think that was also something you were very interested in. So could you discuss what you did or started to do to address what you felt was a particular need here in the OND, and also how that re-org had progressed by the time you left CDER to come to OC?

JW: I don't think that new drugs had modernized itself adequately. And they knew I was not happy. They had had a lot of procedures, which is good. So out of more or less chaos,

they had developed structure and procedures. But what they did, and to some extent they're still doing this in this modern age of electronic submissions, was have in every review discipline the clinical reviewer write a very long, voluminous review; for example, there would be a safety review of perhaps 300 pages, and an efficacy review, or maybe two separate people would do it. And then their team leader would write a review over that. Then they required the Division Director for every new molecular entity to write a review, which often was 20 pages long. And the Division Director may not have been the signatory because that was for the Office Director, so they too would write a review. This is for a single application.

So they had this, and then the toxicologists would do the same thing. And it would be done over in new drug chemistry, which had been reorganized into pharmaceutical quality. They were improving, but they were still writing these. This was a remnant of how things happened, like I said, in the 1980s. The companies would send in these tractor-trailer loads of files that were highly disorganized, and so the supervisors, and these were the Division Directors at the time, had the chemists and everybody in there go—and I called it an archaeological expedition—find out the story of the development program and rewrite it into a long document.

Typically, they really didn't have any conclusions, or many of them. They just retold the story. And then these supervisors would look and they would opine and they would decide what to do. So that persisted, and people liked their work product, but here we're getting electronic data sets of the clinical data. We have an electronic protocol, so we know what the clinical protocol was in the amendment. So we have it all there; you don't need to rewrite it. But were still doing it.

In addition, the offices had been organized by workload so that you might have sheep and goats in the same office. Why wouldn't you have transplant and rheumatology and

immunology in the same office. They're highly related and they often share products. But, no, they were all over the place.

JS: So this was just based on how many applications were coming in for a particular –

JW: They tried to even out the workload by office, yes.

JS: Okay.

JW: And so, for example, I think the transplant group was in with infectious disease, for example. Some of them were closer, and neurology was in with cardiorenal.

JS: And had been for a long time.

JW: Yes, that's right. So I said, well, why don't we really set up offices that have to do with disease areas a little bit more. And, you know, what I did was what I said earlier. I talked to everybody, and there was a lot of pain and suffering. People were very unhappy with the administrative system they had put into place, number one. The project managers were very unhappy. They said we get much better training if we start in CDRH, but we don't have a training program here. A see one, do one, teach one kind of thing. They said we don't have very much authority; we're just treated like scribes. They had project managers whose job would be to go greet the company at the door and walk them to the conference room and then take minutes. And they wondered, can't we get contractors to manage the conference rooms? Because they were double-booking all the time.

Talking to the clinicians and Division Directors told me we shouldn't have to write all these memos if we agree with the findings of the review team. And so I took over New Drugs at some point when John Jenkins retired, and the first thing I did was say, okay, the Division Directors don't have to write these memos anymore. And then I started talking to them about review, and I can say most of the people there at the time did not feel there were any problems.

They thought they were a high-performing organization. And I said, "most of you have watched the development program during the whole IND process. Why don't you start with what the problems you know about are and what the strengths are. Start there when you get a file and meet with the company and talk to them about these things and record that. You don't need to rewrite the history of this whole program. It's all there."

JS: Just one thing, I don't mean to interrupt.

JW: No, interrupt.

JS: There are requirements under PDUFA that things have to be turned around within a certain amount of time. So presumably they are managing to do that part of it. But it sounds like this could be done in a very different and perhaps more efficient way, right?

JW: Yeah, and maybe more effective, because you would focus on the problems instead of writing this long document. And you would talk to other team members about the problems, rather than going off in your office and writing a tome. And then you would deal with the company early on with solutions. Otherwise, what they would do is wait until all this documentation was written, until the eleventh hour. This was the project manager's job,

to manage getting all this documentation done in time before the PDUFA requirement. But, they were doing it at the eleventh hour, because that was there. You would really like to have a couple months to talk things over with the company, and generally you knew most of the problems. Sometimes you'd find a new problem, but you've been watching this program for years..

So I talked to them about all that. I got some people to help me, some early adopters. For example, the IND was phase one. Why don't we have a template? Everybody did it differently. And we have 30 days, we have a 30-day safety review – first in humans. Why don't we have a template? And then we'd have a record and we could look back at the reasons we put on a clinical hold and all this stuff.

And when I talked to them about structural change they were more open to reorganization around disease lines, like, the oncology office. We took the non-hematology group out of oncology, because sickle cell disease is not a cancer. But it was in the oncology group, it was oncology and hematology.

So we started a change effort. I did a lot of listening sessions, and that's where I heard all this pain and suffering. But, you know, there were a lot of people highly vested in doing things the way they'd always done them, including this last-minute scramble, because that was exciting. But it was really dysfunctional, in my opinion. No, it was really dysfunctional, because sometimes senior managers five, ten days before approval would learn about a problem that everybody else knew about the whole time, but they hadn't been apprised of it. And often it would delay the approval and miss the user fee date while the senior manager had to work through these issues. So we got support from contractors on change management, on getting all this reshuffling of the people done. We talked, we got the project managers and pulled them into a centralized organization so that we'd have uniformity in how they conducted their business. All this would cause tremendous suffering.

We developed templates for the IND, and we also got a program for team review of the NDA, where everybody would sign the review and they would contribute pieces of it. And, you know, that caused some problems, many problems, and I think they're still working on it, but it was to be short. But of course then they still wanted to have these tomes in the background, but at least we would have a summary basis of approval that would be succinct. It was supposed to be problem-based rather than just indicating in phase one they had 20 volunteers and then they did a phase two program at these sites, and so on. You know, that's not relevant really, and it's in the documentation the company sent. So there's no reason to reiterate all the stuff. So that helped, I think, and some groups have adopted the shared review, you know, the team review, and that has really improved communication and so forth amongst the team. And also, you know, it presents, like I said, a summary document that's a summary basis of approval, which we're supposed to publish then. And we used to publish all these tomes.

So anyway, but in the end, Peter Stein came in as a director, but I'm still kind of overseeing and driving this change. But then COVID came and I went up to Operation Warp Speed as the therapeutic lead, and so I kind of lost track of that. I think they were overwhelmed with what they had to do. They had 400 INDs or something like that on top of their ordinary list of stuff. Plus they had to do a lot with hand sanitizers and all these things. A huge amount of work was put on people during COVID, and I think some of the momentum of that reorganization slowed.

JS: Had they started to witness changes in efficiency with those groups that were realigned?

JW: I don't know how far they got by the time I left, but between Warp Speed therapeutics first and then as Acting Commissioner, I had bigger fish to fry. So I never went back to CDER. But I do understand that it never fully . . . I mean, you have such culturally ingrained practices;

Part 2b 22 July 2024 240722_003: 00:20:17

JS: Some of those divisions had been fixed that way for a long, long time, and it was very hard for them. But some did change, though, you said.

JW: Yes. There was change, yeah, and I think there's adoption, and Patrizia's had to work on a new computer system, because that's the other thing. I had built that division file system, which was the first electronic system. It was basically a document filing system in the late '90s and everybody had to use that for FDA stuff they generated. That changed into DARRTS (Document Archiving, Reporting and Regulatory Tracking System), and then they had customized IT extensively, which is so funny because we had to force them to use the division file system.

JS: But DARRTs is still around, isn't it?

JW: It's being phased out is my understanding. It's hard to give up, but it is the back-end filing system; it isn't really a workflow management system. That's the problem with it.

JS: I have just a quick question the Cures Act. The 2016 21st Century Cures Act had a huge impact on FDA, of course. What was your role in bringing elements of this into being

and implementing these into the law? Including things like the use of real-world evidence in our regulatory decision-making, as well as things like enhancements to improve antimicrobial drug development? All the hiring and retaining of staff that the law changed completely must have been a huge lift.

JW: I wasn't really involved that much in the real-world evidence because outside parties were very hot on that and were really pushing that. We tried to sort of moderate expectations on the Title 21 expansion. I was very deeply involved in that. That was a really tremendous benefit to the Agency, and getting that for foods and the field and so forth was just really important.

I was the lead on trying to get antimicrobial development through. I don't know how much help that has been because the pipeline is so small. It's really hard to develop new antimicrobials, and maybe biologicals are possible. But with the small molecules, it's just been really, really difficult. And companies set up programs sort of altruistically and just lost hundreds of millions of dollars, never having come up with anything. So the problem is that the pipeline, even with incentives, is not that good. But I think the LPAD (Limited Population Pathway for Antibacterial and Antifungal Drugs) is helpful in getting treatments out there.

JS: Okay. We've talked a little bit about selected drug evaluation decisions that have been made through your career. I think the last one I want to bring up was the approval of a eteplirsen for Duchenne's muscular dystrophy. The review team, the OD Director, and even the advisory committee did not recommend this approval.

JW: Right.

JS: You did, of course, and I wonder if you could discuss why and what was the reaction to your decision, both by those within the Agency, but also those outside, like, the patients and families, those affected by the disease.

JW: Well, this was a very marginal case. It was a targeted therapy for a very small number of individuals with the disease. So it wasn't for all people. As I said earlier, targeted therapy subsets the disease into multiple different subsets that have different molecular etiology. So this was targeted at a specific mutation in the dystrophin gene. And there are many, many, many. So I don't know how many kids, but it was under probably 2,000 kids in the United States that would be targeted by this.

As I said, the company had not done a very good development program. On the other hand, it's very difficult to study something like this because, they don't want to treat babies. Older kids already have this giant inflammatory process going on, even at five or six years old. They have a huge inflammatory process going on, which is destroying their muscles. And so this particular intervention was supposed to facilitate transcription of the gene, where ordinarily it would be stopped by patching over part of it. And that meant it had to be given all the time to the kids, and it had to get into the muscle, and it had to cause more dystrophin to be produced. And how do you study that in the kid? You have to get their muscle and look at it. And that's very difficult with a child who's losing their muscle and going to lose their life because they've lost their muscle. How do you actually do surgery and biopsy their muscle?

In fact, even if you biopsy it, you don't have a baseline of how variable it is across the person's body, because you can't do multiple biopsies of a child who's dying from muscular dystrophy, although it takes them about 20 years to die, okay? So the company had done biopsies and, they hadn't done a very good job. I got somebody in the biologics part of

CDER, a protein chemist, to look at their data and so forth. It looked like they were causing some dystrophin to be produced. Now, the argument was about how much dystrophin would be enough. That was the whole argument. And, you know, also probably the division wanted more dystrophin, more subjects than what they actually had, before and after.

But originally the division had said we want 50 percent of normal to be produced, okay. I knew there's a condition called Becker dystrophy, which is a milder form of dystrophy, where they produce some. And they might be down in the teens, maybe even the 10 percent, and they still have a milder phenotype.

So I said, why can't we go lower? So they grudgingly said, yeah, we can go lower, but not lower than—I forgot what they said—10 percent or something. The company did not have a really good estimate of how high, but it was clear they were producing some. Now, it's clear from my view—the literature was clear—that any amount of dystrophin more than zero would be somewhat helpful. And for these kids, if they were in a wheelchair, they would be able to manipulate a computer or mouse to communicate—they might be on a ventilator, to play games, to be part of society, that was a meaningful benefit. And so I said, “It looks like they're producing some.” I wrote a memo that it looks like they're producing some dystrophin. And, in my opinion, that is likely to predict clinical benefit, so I went ahead. But I agree, that was a very marginal case, not because of my reasoning, but because of the small number of people that they had before and after.

So, yeah, New Drugs did not agree with this, and Ellis Unger appealed this to the Commissioner, and there was quite a uproar. People gave me a very hard time (laughing); the Office of Chief Scientist were very rude to me. But, ultimately, Rob Califf was Commissioner at the time and he upheld the decision because the appeal was supposed to be procedural, and that's what the procedure said. It wasn't supposed to be substantive above the

Center because that would put decisions in the hand of a political appointee, and procedurally, there was no issue.

This was a substantive judgment call issue. So that's what happened, and they were quite unhappy with this, but the Center's gone ahead and approved a couple other exon skippers based on demonstration of increased dystrophin.

The company was supposed to do a confirmatory trial. They're doing it in a different targeted therapy, to a different part of the gene, because once you approve something, you're not going to have kids who will go without. So they were doing a trial, but then COVID came along, and I haven't heard about the results of that trial. CBER just approved a microdystrophin gene therapy that produces some dystrophin in the kids. I'm not sure if that was an accelerated approval or full approval, so it isn't known, really, how much dystrophin would need to be produced to provide a meaningful clinical benefit, and I'm not sure how you would find that out.

JS: Where did they come up with this 50 percent level in the first place before you had approached them?

JW: Well, I think that was their comfort level. It's unrealistic that an exogenous therapy would be able to do that. I mean, that would be hitting it way out of the ballpark.

JS: Okay.

JW: But that is my recollection, at least, of what they had said that would be needed, 50 percent. But then they backed off on that when pressed, because the Becker phenotype obviously is much lower than some of them. I found cases in the literature that, as I said,

were in the teens, at least 10 percent. I documented all that in my memo. Those people did a lot better, though. So the question is, isn't that a clinical benefit?

Now, an exon skipper doesn't produce the exact same dystrophin, because you've skipped a little part of the gene. It's a huge protein. So it does some other things; it has other enzymatic type of activity. So in different areas you might skip something that was really important and that might not work. But the gene therapy was approved by CBER recently. And of course with gene therapy, you do it once. That's all you can do it, once or twice. And so the question is persistence if it actually improves things. That's something I'm working on now for very rare diseases—how do you really study them? What should the standards be? Because we can't look people in the eye and say, "Your child's going to die. We'll never have any treatment because the programs can't meet our standards." You can't do that.

So, people had quite a grudge against me, but I was okay with that. I just did what I thought was the right thing to do was; scientifically, legally, and so forth.

JS: I know you've had a long interest in information technology in the Agency. When you were the Principal Deputy Commissioner and Acting Commissioner you oversaw the transformation and expansion of what became the Office of Digital Transformation. What were some of the problems we had in this area prior to this, and how has this office addressed those problems that we had?

JW: Well, there are long-standing problems. The Agency had never had a strong central IT, and John Dyer oversaw reorganization of the central function, which most people, including me, thought this was never going to work; and it caused a lot of problems. But they were never that strong. When I took over as Acting Commissioner, they were reporting into the Office of Operations. And FDA's an information Agency. Sure, we're a law enforcement

Agency, we're a science Agency, but we do that through processing scientific information and other information. And we need to have up-to-date IT support for that, but we didn't. And yet we spend a massive amount of money on IT. And the reason is every single Center or group has developed their own IT.

And so we have all these server farms all over the place, data centers they call them, that support these different applications that everybody's developed. So everybody wants their own server. We had servers that were running 10, 15 percent capacity. But what is now ODT, that office had to support all that stuff. There were hundreds of them, and people don't understand that. They were always complaining about the cost of the IT. But you do it this way, it's going to be very costly. And yet they persisted in doing it.

So the first thing I did was to elevate the office, have the CIO report directly to the Commissioner, which is how it should be, then I said they had to enforce CIO sign-off on any new application development. That's how it's supposed to be. I ordered an inventory of all IT programs and development across the Agency—the first time it had ever been done.

And that was very, very eye-opening. We found applications and programs that had never been reported to the CIO. We found all kinds of duplication and problems causing a huge amount of expense and so forth. Actually, it was my review of ORA's IT programs that caused me to be very interested in a reorganization of ORA. But anyway, they became ODT, the Office of Digital Transformation, and they really tried to step up and become what they needed to be. Their security under Craig Taylor has always been very good. We've always had very good security, but control of the applications and developing a common infrastructure, including application infrastructure, had never happened. They really didn't have application developers. They didn't have data architects. So how were we to find people? We didn't have a data architecture.

I enticed Meredith Chuk to come to Warp Speed to oversee the distribution to hospitals and so forth of the therapeutic monoclonal antibodies for COVID, because they were having huge problems. And she straightened all that out and got them distributed.

When she came back, I inveigled her into running a small program, reporting to me, that would build an inspection platform. That's something that the Agency's crying out to have. We never had a platform where the people can order inspections, can see who's doing the inspections, can see when the inspection is progressing, can receive results back. Ordering inspections was done by email or, you know, fax or whatever. Inspections were signed manually by the districts. Still are. And then the results were kept within ORA, and then eventually sent back to the relevant office in the Centers. You know, this is by no means a team effort.

So Meredith set out to build a platform that would have everybody working off the same workflow management platform, and it was a huge process. They selected Appian as the platform they would use and they spent years, a couple years, because there was some intransigence there, developing a way for the inspectors to use a laptop. No, a tablet. To use a tablet to go online with program and do their inspection in the plant so that they're not double entering the data. They needed an offline version, because we have to go offline in China and here and other remote areas. So that took a long time. For ordering an inspection, who are the people ordering it. Then assigning the inspection—who does that in ORA, and then doing the inspection and collecting the results. And then ultimately sending it probably to CMS, the Case Management System that ORA operates for the compliance efforts if they're needed. But none of those pieces were connected. In 2024, today, they are still not connected. I did my best, but I couldn't get it all done. There was huge drama and resistance, and still is to my understanding.

Part 2b 22 July 2024 240722_003: 00:41:20

JS: Will the change in compliance offices, moving back to the Centers, have any impact?

JW: That will cut out one step, which is a very good idea. The Agency hopefully will speak with one voice as far as their compliance philosophy and their approach. But it doesn't help ordering up, assigning the team to do the inspection, prioritizing that, doing the inspection, and so on. It should all be on a workflow management platform, and trust me, it is not. But when I was Acting Commissioner, I started building that, but these things take time and they're very painful. ORA has this e-inspect, and they want to keep doing that. They have their own IT. The field was doing a huge IT development program, and had been for years. So that was one of the things I did along with this reorganization, which we haven't talked about.

JS: We are getting to that. But before I do, I want to talk about your early work on COVID. So obviously you were involved in the Agency's response from several standpoints. You started the Coronavirus Treatment Acceleration Program, and you moved on to lead the therapeutic developments under Operation Warp Speed. Could you talk a little bit about that, because you had just started CTAP, right?

JW: Sure. Did we talk about hydroxychloroquine?

JS: Not yet, but please do.

JW: That was one of the first things that happened. I mean, we were trying to deal with hospital shortages in the first part of the pandemic because hospital supplies were running out, ventilators, you know, the drugs you need to keep people on a ventilator, all that kind of stuff was just totally in short supply. And hydroxychloroquine was getting in short supply. And it's needed for people with lupus especially, who have a very serious disease. And then the President (Trump) accepted a donation of a large amount from a firm into the stockpile. But that drug was somewhere in Asia. And so there was a huge uproar about that and it hit the papers because of Rick Bright, and because I think the administration was flailing around quite a bit about how to make that available. They were going to do an IND, and they had all these people involved and all this kind of stuff.

So I decided we would have a EUA, Emergency Use Authorization because then we could control this. It was done just for hospitals. Not everybody and their brother could get hydroxychloroquine, it was for hospital use. There was data showing it had some antiviral activity, which turned out not to be the case, probably. I mean, it did, but it wasn't substantive in the sense that it would help.

Hydroxychloroquine has some problems with QT prolongation and so forth. So, we put some stipulations on that and we were able to make it available to hospitals. And we had to get this and test it to make sure it met all the criteria for quality. So we did that as well. Then that was imported, so hopefully lupus patients then could get their hydroxychloroquine. That EUA was subsequently withdrawn when it was shown that hydroxychloroquine is not effective against the virus, at least for people in the hospital.

There was a lot of controversy about that. Rick Bright—the head of BARDA (Biomedical Advanced Research and Development Authority in HHS)—filed some kind of complaint about pressure that was put on him regarding hydroxychloroquine. And he said there was pressure on me, too, and that we fought it. We did oppose lame kind of programs

to distribute this to everybody and their brother. It's not a benign drug. It also causes retinopathy. Yeah, but for people with lupus, it's, you know, under good supervision or people in the hospital with COVID, okay, because there was nothing else at the time, there was nothing. But so I just wanted to make it clear. Yeah, I authorized that, and then it was withdrawn. We tried to have a very controlled program for distribution of hydroxychloroquine.

JS: But there were data that suggested its antiviral activity.

JW: Yeah. It was in vitro, against the COVID virus. But our top clinical pharmacologists thought it was reasonable at first. And then they looked at more experiments and they said not enough gets in or whatever, it's probably not going to work. But then there was clinical data emerging that was not effective. So anyway, that was that episode. But we had CTAP, the Coronavirus Treatment Acceleration Program. That was fine, I think, for me to leave.

Poor Patrizia had to deal with everything but she's perfectly competent to deal with that. It was really a program in which we would pay extra attention to anything that really had some merit in working against COVID. And that of course meant some of the more ordinary stuff got a lower priority. But given what was happening, that made sense. They also had to deal with so many things, but they did a very good job. I feel like CDER had been set up in a way that was highly functional. They dealt with shortages, they dealt with hand sanitizer issues. And they got that all done. They issued all kind of guidances, all kind of exceptions to different ways of doing things, like telemedicine, to accommodate the pandemic. They were very stressed, but I think they did a good job. They did fine.

So, yeah, I went up to Warp Speed as a therapeutic lead. And that was a different kind of experience. But we got some monoclonal antibodies out for treatment, especially for

immunocompromised people. Even once we got the vaccines, people were still coming down with COVID and needed treatment. So, I think it was worthwhile and we learned things. We learned that during the hospital phase, which is a sort of immunologic storm, that these antibodies were not helpful. And probably convalescent plasma also was not in the hospital phase.

JS: You returned to the Agency as acting commissioner from January '21 to February '22, running the FDA in the middle of the pandemic, but also overseeing the ramping up of the vaccine program, the vaccine boosters, everything else that we were involved in. That would have been overwhelming to most people.

JW: It was pretty much of a firestorm, because like I said, when I came in, I had to elevate the IT people. We had a crisis with vaping. We had 6.4 million applications that the tobacco center had no plan to review by the next year when the judge and all the outside world expected them to be done. So I intervened in that and got the majority of them taken care of, although I think the standards issue is still up at the Supreme Court, or will be. There have been lawsuits about that. For most of them the FDA's position has been supported because we have millions of children who have been addicted to nicotine because of vaping. Because of the statutory standard you're going to have to show your products is appropriate for protection of public health. You're going to have to show the bubblegum flavored vaping juice is appropriate for protection of public health. In other words, that the benefits outweigh the attraction to children. Most of these flavored bubblegum and candy and other flavored vaping juices would face a pretty high bar.

So we went ahead and said that unless there's some showing of benefit to somebody to weigh against this harm that has been caused, they're not going to be approved. So, you

know, I think that's a pretty common sense kind of standard. But that was a huge effort. I had to talk to the Chief Counsel into that, and I had to talk to the Justice Department as well.

And then, yeah, there was all the drama around vaccines. There was drama around some of the therapeutics like Paxlovid when that came along. And then toward the end, we had the issue with infant formula.

JS: That last issue was interesting in many ways. Could you say a little bit about that, if because it does segue into one of my last questions about reorganization efforts and the Human Foods Program?

JW: There were some reports of infant death, and those infants had a bacterial sepsis from a bacterium, and they had used Abbott formula. But then most infants, a large number of infants, use Abbott formula. It turned out upon investigation that it came from a certain production plant.

The inspectors were just in that plant the day one of those reports had been received. But as I already told you about the computer systems, they were not communicating. And apparently there had been an outside whistleblower complaint that had been sent to the Agency about this plant. I was cc'd on that complaint but we checked with everything, the document room, everything. We had never received anything addressed to me for this. It had gone to OSHA apparently, and OSHA had sent it to a mailbox that OO manages, but the person wasn't there because of COVID, or something like that. And then I guess somebody in the field got it, but I'm not sure. But again, those things weren't known.

So once everybody synapsed on this, I think this is the chronology, but it's all very well documented. The inspectors went back and they did environmental monitoring. They found five different strains of this bacterium with just one visit of environmental monitoring.

And they found records that actually there had been lots fouind with this. And of course they'd been discarded, but the lots account for tons of formula and they get a few grams and they test it. It's not really a good sampling strategy, shall we say.

Then, when the inspectors went in there, armed with knowledge and complaints and everything, they found a lot of objectionable conditions, including the fact that this bacterium had shown up in a bunch of lots. And so we started discussing, doing more intensive investigation, including those five environmental samples. I mean, that was really problematic. And so we started doing a lot more investigation and determined that the plant really needed to be shut down because it was too out of control. And that, of course, we knew would trigger shortages and we thought we needed to do a recall, too, because of the sampling results.

So we did. And that was the day, I think Rob came in the day we got the recall done. But, I think there was difference of opinion within the Agency. Some people didn't think we needed to do either of those things. But it turns out they tried to restart their plant numerous times and then they had to shut down. They couldn't make the formula without contamination. So, they had to do a very major overhaul. And it was an aging plant and so forth. The recall and the subsequent shortage caused tremendous attention. And Rob was very unhappy that I put this in his lap and President Biden had to get involved because there were shortages and pictures. And as soon as the television shows show pictures of empty shelves and everybody goes out and buys, and then that exacerbates any shortages.

But they were real shortages and they had to fly formula in from other countries and we had to make sure that it met our standards. And, you know, it was expensive and politically unpleasant. But we got through that. But that took a lot of my time, too. And that resulted in a call for the foods program to be re-evaluated.

JS: Which is not the first time this happened.

JW: And then there were calls for the tobacco program to be re-evaluated due to all the problems with vaping. They had some other problems with one of their applications. So then I had started to take that on with Melissa Safford, who works with me. Rob asked Steve Solomon to do a report, an evaluation of the infant formula incident. So that was done and that revealed additional issues.

And then there was a call for the Reagan-Udall report to be done, which Jane Henney, former FDA Commissioner, led. And the Reagan-Udall report had a number of issues about the tobacco program. But they also recommended that the foods program be reorganized and that ORA be abolished and spread to the Centers; they were talking more about the food inspectors belonging to the foods program. My position, which was fairly well known, was that this is a bridge too far. You know, I could do a lot in reorganizations, but, you know, it's only so much. And that ORA should be kept together, but it really needed a complete overhaul. So I got a group together of these sort of early adopter types, some people from ORA. Some of them were early adopters types, and some of them were senior people. But we started meeting every week for hours. And I also did more than 50 listening sessions with all the staff.

JS: Are you talking about ORA only?

Part 2b 22 July 2024 240722_003: 00:59:42

JW: No, ORA and Foods, and the compliance officers in the Centers. We made an imaginary country called Rigatoni, and Rigatoni had states in it that had foods program, but it

had no central foods program. We discussed how we would devise a food safety program for Rigatoni if we're starting with a clean slate? It just seemed to me there was too much baggage talking to all these people. There'd just been too much going on. We talked for a long time and we determined that a Foods program is really about risk management to a great extent, because it's a post-market program.

Okay, so how do you do risk management? Then, part of what I heard from the foods program is they had too many issues, which is true. They're way understaffed for their remit. They would work on something for two months and then they'd be told we have to work on something else, and they would be shuffled and they'd never finish anything. I did a lot of talking with the outside world, too; those behind the Reagan-Udall report also had interviewed the outside world bunch.

So through that process we arrived at a new vision for the Foods Program: that we'll move the foods parts in ORA. They had the state relationship, which is huge in Foods because they do the retail. They do a lot of inspections on all this. We'd move that back to the Center, Federal-State Relations, and so forth. And we would eventually, with Namandjé Bumpus's help, figure out what to do with the laboratories. We would move the food laboratories back to Foods. I had asked Namandjé to help me and deal with the laboratory issues because there were tensions between the Foods program at Central and ORA foods labs and the state labs. And all three of them were none too happy.

We needed to look into this and figure out how to resolve these issues. So she did that and arrived at the fact that the field food labs needed to move to Foods. Then the other labs stepped up and told her they wanted to move under the chief scientist. Yes, the other field labs, which were not food labs.

JS: They're the ones that suggested moving under OCS?

JW: Yes. Oh, absolutely. They all supported it. So that happened. We put that into the plan, you know, told everybody. There was a lot of uproar, but that was the right thing to do, frankly. ORA should stay together, but they should focus on inspections, investigations, and imports, right? That's huge, a huge global remit, They don't need to be IT developers and state relations.

JS: What about recall coordination?

JW: Well, they had all these – and there were many people in ORA who proposed reorganizations to me. What had happened with ORA is they'd done that PAG, a program realignment, where they were gradually doing away with the districts and specializing the inspectorate. But the districts had all these other functions attached to them. It was, like, feudal in the past. The district was the hen and there were little chicks, like the state relations. They had an emergency coordinator, they had a recall person, they had this and that. And when this PAG was done, those functions had not been rationalized. So they were still attached to districts – thought these weren't really districts anymore, or they might work for a Foods Program person. And that's kind of what happened. The consumer complaint coordinators who got the complaints from the infant formula weren't a single group, and there were a whole lot of problems with that. I won't even go into it. But they were attached to different people, and so it just relied upon who they knew and who they could call to tell what had happened. Even they were taking drug adverse event reports they put them into FACTS, not MedWatch. This is, like, 30 years after MedWatch had been founded.

So a lot of functional reconciliation had not been done in the field. Nobody really looked in the field and said what is this organization supposed to be doing? They had a large

training group, but they have a giant training remit, and it was great unhappiness amongst all parties about the training and so forth. So first we did the Foods Program and looked into what the Foods Program should look like? Okay, we'll move the state relations over, we'll move the labs over, but we'll leave the inspectors in the field—but they're food inspectors.

So then we looked at ORA. How do we actually reorganize ORA? For example, emergency coordination was in OO, but the operational part of emergency coordination is in ORA. Why doesn't ORA run emergency coordination, right? OO can take facilities, like central facility emergencies and so forth, but most of these emergencies they were coordinating were outbreaks or a train derailment or other things involve production plants out there.

Then we said, what about the complaint coordinators? Lee Cohen, who worked for me, did a deep dive into that and found that we have thousands of points of entry for people to send in complaints. And so she's working on that, but we ought to have one number to call—a call center—but we had a thousand. With the infant formula event, with this person called them and they called that, it just showed it was happening all the time, and it's a huge vulnerability. Then we had the recall coordinators and how we manage recalls. Well, the Center said we manage the recalls. ORA said we manage the recalls. So we had to sort through that. And we had state liaisons—where do they go, and there were different kinds of state liaison jobs. So, we had to sort through all these things.

During that time, I think the leadership of ORA became very unhappy with me and complained to Rob and so forth. They said I was being mean to their people and everything. I don't think I'm ever mean. I don't know. I mean, I've maybe lost my temper once in the whole time I've been at the Agency.

JS: How is that possible?

JW: Because I'm just very calm, and what good is losing your temper? Even when I lost my temper, I controlled it. I mean, there was a division and they did a terrible wrong to people with dying children. It was just so awful, and I got the FDA pediatric ethicist involved, and he agreed with me. But, I didn't shout or raise my voice. I just was very angry.

But usually I don't find anger helps you at all. I'm not rude. I just told the people in ORA that the Reagan-Udall report said you should be abolished. Did you read it? I'm not going to support abolishing ORA, but you have to really change. And so I guess that was mean, but I don't think so. I think they needed the message.

So, anyway, then we had to lay out all these changes. For changes like these there's this giant group in OO – I call them the organization police, and you need have your spreadsheets for change color coded. It's gigantic. And then of course you have to reconcile the budgets. And I will say in OO, Angel Herbert and company took that in hand and they got it done. I don't know how they got it done. Jen Wade did the financial part of this, and we got this giant re-org package. Before I left, we had it done and submitted to HHS for review.

So at the same time, of course as we've discussed, we had to put in place a change management program. Now, ORA had had a contract for change management. They gave us some of that, a little of that. I don't think their heart was in change management at the time. Their heart was in sort of change resistance, so that was difficult, but we put it in place. We wanted to get all the early adopters together and all the volunteers. They lost a bunch of their funding when I left, but I hear the change program is still going on.

JS: Oh, it is.

JW: Oh, good, good. Because that should be a way for people to hear what the troops are saying and then get messages out in a more personal manner by people who believe in the change, who understand the change, but it is a huge transformation. It hasn't totally happened yet.

Now, in my mind, all this should have been done a long time ago. None of this is very innovative or anything like that. This should have been done, these things were marinating a long time with big problems.

And of course Jim Jones came in as running the Foods Program, but it's not going to end up at that level of efficiency and effectiveness as, say, CDER, because they've not been well organized for quite a long time. And, you know, they're going to have to pull themselves up and it'll take quite a while. Plus, there is still considerable resistance, I think, in ORA to these changes, a lack of understanding. And that requires dealing with.

JS: Well, the changes are coming nonetheless, though.

JW: Yeah, but as I said, you change the boxes around. That's the least of the effort. The real effort is to get the people to act a way, the new way, and if people spend much of their time resisting, they can create a lot of heat without very much light.

JS: But I'd be interested, if you care to share your opinion if we encounter another serious food problem, what do you imagine could be the impact after undergoing a change like this? Not that this change is made so that we'll never have another problem like this. But these problems, as we know here in FDA, often generate a lot of heat, as you said previously.

JW: First of all, they're setting up and got resources to set up in the Foods Program a centralized complaint triage group. They had some of that, but the ORA was off doing their own stuff. Theoretically, all complaints should come in there. The immediate ones that are serious would be handled immediately. They wouldn't be going through ORA channels. They would be in the right place to react, evaluate and react, okay.

Their management chain is very clear-cut now. It isn't distributed amongst three different parties. So once any serious issue is elevated, they should be able to respond quickly and be on top of it. Their core group is part of an emergency management, or will be, when the reorganization goes in, part of an emergency management group that can be brought in and stood up really quickly to handle some kind of problem like that. So I think those are structural things that were impeding the organization. All the people were good and had the best intent, but they were in a structure that was not very functional and impeded rapid evaluation and response. People were in different parts of the Agency, were doing different things and couldn't communicate with each other. They didn't have ways to communicate.

So I believe that they will be set up for detecting and responding rather quickly. And like I said, they're good people. They want to do that. Plus there was a lot of emphasis on putting the correct expertise on the problem right away. During the infant formula crisis, while it was sort of marinating around, CFSAN had two experts in infant formula manufacturing. I mean, they weren't involved until this whole thing blew up--why? Because, the inspectors talked to their compliance group in, ORA.

So now with essential compliance in Foods, if there's a problem then hopefully they will be in a position also to immediately elevate it to the experts. In other words, streamlined in opening up channels of communication. The goal now is that the inspectors, if they find something, they can call headquarters and talk about the implications while they're in the

plant or while they're doing the inspection. They don't have to call in the plant. They can go out somewhere and have a call with headquarters and talk and get the experts involved to find out what this means. So everybody's on the same page from the beginning.

Hopefully this will work. Again, there are many people who, for their own understandable motives, are going to try and make this not work. I think in the Foods Program, though, there's quite a bit of unity of purpose, because we spent a huge amount of time on the effort to devise a new program, and we actually implemented the program that was devised. It is being implemented.

JS: I understand a lot of these changes are going to be stood up within a few months.

JW: Yes, that's the hope, I think, yes.

JS: So this was one of the last things you were involved in here as Principal Deputy Commissioner.

JW: Yes.

JS: We've covered a lot of issues in these two sessions, but I do want to ask if there are things that we really should have covered that we haven't. I know there are some that might stand out in your mind.

JW: I don't know. I mean, I've been involved in dealing with so many problems. That was the nature of the job. Obviously what people remember are the crises like heparin, like Vioxx,

like rosiglitazone, you know, the things that get in the media like opioids and so on, and the legislative milestones. We didn't talk about getting the OTC monograph.

JS: We did not, which reminds me of a testimony opportunity you had, and it had to do with monographs. I can't remember which member of Congress it was on the panel asked you why aren't we changing things. And I seem to remember you reminding them that it's not up to FDA to change the law. And then there ensued a rather spirited discussion among the lawmakers. What's FDA's responsibility here in creating changes?

JW: That's interesting.

JS: That was an eye opener. But anyway, the monograph series has been an ongoing challenge.

JW: We got rid of the monographs and got administrative orders because CDRH already had those for certain things, so it was something that people knew. And then we put in place allowing new things to go into this new system, over-the-counter system, which makes a lot of sense, too. And we got user fees. So it was a package deal.

So that program—because we had calculated that at the current rate—of modernizing monographs with current science would take us a hundred years. And by then, surely science had advanced. They'd all be out of date. Peter Hutt was really a problem for us because he kept saying, “Well, when I was at the Agency, I would sign regulations into law.” Well, that isn't how it works anymore, Peter. He couldn't understand why we couldn't just do this. But come on, have you ever heard of OMB? Domestic Policy Council? I mean, these things

have existed for a long time. So, yeah, that was, I think, one of the final cleanups we had to do at CDER.

Part 2b 22 July 2024 240722_003: 01:20:12

The problem is that even now, regulations and laws that were passed long ago are outdated for current science. And so the Agency spends a lot of time doing workarounds. But now, with current jurisprudence which demands a lot of fealty to the original statute and its intent, we're losing more because we actually are trying to adapt that old law to modern events and modern science. And it doesn't work.

But it's very difficult to get Congress to change. So I feel like I was pretty successful when I was at the Agency at getting change, at driving change to all these things, getting new laws and everything. I understand our General Counsel's Office has always been reluctant to open up the statute because they fear mischief. But you get to a point where the pain of trying to adapt these statutes to modern realities is greater than the risk of them doing something strange. So I feel that's an ongoing issue. I think there's really a lot of problems with current law and its application, for example, in modern ultra-rare diseases. But, yes, that was another one, monographs.

So with every reauthorization of User Fee Programs we've been able to put additional tweaks in. And that's been a great opportunity to put in policy, get new law, get laws modified, and so forth because that's must-pass legislation.

JS: Well, I really can't thank you enough for sitting down and sharing this long journey with me.

JW: Yeah, it's interesting to me.

JS: To me as well. And I guess unless there's anything else that you'd like to bring up, I'll just thank you again and wish you all the best. I know you have a very busy life outside the Agency as well.

JW: Thank you, I was happy to do this.