History

of the

U.S. Food and Drug Administration

Interviewee: Mathew Thomas, M. D;

Interviewer: John Swann, Ph. D.

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INDEX:

JS: My name is John Swann from the FDA History Office. I'm here with Dr. Mathew Thomas conducting another in our series of Oral Histories. We are at the White Oak Campus of FDA. The date is June 13th, 2023.

Mathew, thank you so much for agreeing to do this. This is about the last week of your tenure, at least on site at FDA. I appreciate how busy you are, but to take time out to do this is very much appreciated. But it's something that we really wanted to do. You've been in so many different positions in FDA and been here for quite a long time, too. I'm looking forward to hearing more about this. So, I would like to start at the beginning. You grew up in India and had your early educational background there. And I was wondering what kind of interests or inspirations you had to pursue a career in science, and medicine particularly.

MT: Well, let me begin by thanking you, John, for this opportunity. I really feel so honored to be able to sit down and talk to you a little bit about what I recall from my journey through life in general. So, you are starting with a question about what got me interested in science, and in medicine.

So, in India, the educational system, at least when I was growing up, is that by the time you finish your high school and your pre-university education, you choose a track of either science or math or economics. And so, I chose the science path, and it led me to apply for med school.

I got into med school, I finished my medicine in the Madras University, which is in the south of India. And then fate had it that I got married to a lady who was born here in the U.S. So,

I immigrated to the U.S. in ‘83 and my first [meaningful] opportunity was to work as a research assistant at the Medical College of Pennsylvania.

And I started working in lipid research, particularly studying lipid protein interactions. And that was a time when I know there was a lot of interest in lipids and lipid-altering medications. So that was a nice area for me to work in. And so that's my - was my early interest in science.

JS: Right, and so was it quite an adjustment for you, moving to Philadelphia?

MT: Not a whole lot. Obviously, when I came here, I had two paths that I could have taken. One is to get into clinical practice and clinical medicine. I happened to stumble upon the research track and so that is what I chose, which I thought was much more rewarding, I studied in English medium schools from my kindergarten all the way up through med school and everything was in English. I did not have a problem with the English language. And I consider myself as a person who is very accommodative and adjustive, so I did not have any problem fitting in, through my journey and getting into Medical College in Pennsylvania where I worked for about five and a half years. Close to five years.

JS: Right, right. That position as a research assistant segued into a fellowship, a resident fellowship, right? At MCP.

MT: That's correct.

JS: And that kind of got you entrenched in the development of multi-center clinical trials.

MT: That's right.

JS: And all of the stakeholders that are involved in that, patients, the physicians' industry and so on. And it, in some ways, one could say that this part of this certainly must have informed your subsequent career because you spent so much time around individuals like this and that sort of thing.

I'm wondering how this came about, how that change, your change of position happened and, maybe a little bit more detail about the role you had and what lessons you learned from that experience, because often these early experiences are so formative in the rest of our careers.

MT: One theme that I would like to think of throughout my career, from early on until now, has been that there's some kind of a force, I guess some people may call it God, I believe it's God, but others may think it is some kind of force or fate that has always guided me from one step to the other.

I can go on narrating so many incidents that made me that way. My coming to Medical College of Pennsylvania itself was just one of a happenstance. I met somebody in church who

introduced me to someone who was in Medical College of Pennsylvania, and he said, “Why don't you come and work with us?”

I ended up there and then as you mentioned, I started off as a research assistant, and then Medical College of Pennsylvania was starting a lipid clinic, with a doctor called David Capuzzi, who was, at that time, quite famous in the Philadelphia area. So, he one day just walked into my office one evening and asked, “Who's Mathew Thomas?” And I said, “I'm Mathew Thomas.” He said, “I am looking for a fellow. Can you come and work with me as a fellow?” And so, I said, “Sure. If you can give me that opportunity, I would love to do it.”

So, I worked with him as a fellow. It was a one-year fellowship. And incidentally, during that period, he was invited to speak at the FDA because of his work. And he volunteered [asked] me. He said, “I have a fellow who can come and talk.”

And so he just said, “Mathew, you're going to go and do it.” So I came here, to the FDA, and did a presentation on my work to the Division of Metabolism and Endocrine Drugs.

JS: And this was while you were in the fellowship?

MT: That was during my fellowship. And it was a time when I was almost ready to finish my fellowship. If I remember, the date of my presentation was June 15th, 1989. And then incidentally, this June 15th [2023] is going to be my farewell party.

But that aside, I was finishing my fellowship in July and I was actually, because of family situations, I was planning to go back to India by August. My dad was alone, my mother had

passed away, and so my plan was to go back. But, just advancing a little forward, after my presentation, the person who invited me, Dr. Ross Pierce, who was there at that time in the Division of Metabolism and Endocrine Drugs, Dr. Ross Pierce asked me, “Have you considered working for the FDA?” And I said, “Not at all.” I said, “If there's an opportunity, let me know, but my plan is to go back in August.”

Well, long story short, he discussed it with his boss, and they invited me to work as a visiting scientist in the Division of Metabolism and Endocrine Drugs and I joined, I believe, August 28th, 1989.

JS: Wow. Did you have any, in terms of your work overseeing clinical trials at MCP, did you have any connections with FDA?

MT: Nothing. Nothing at all. I had no idea what FDA was doing. I mean, I knew of FDA and we were always worried about FDA coming in for inspections and stuff, but other than that, I had very little understanding of what FDA was and did, until I got closer to coming here.

JS: I imagine that was a pretty good excuse to familiarize yourself more with the FDA.

MT: That's right. Right, right.

JS: Before getting into the work, the nature of the work you were involved in, I kind of want to get your sense of when you arrived at the agency, it must have been at the Park Lawn Building, I'm guessing, in Rockville.

MT: That's correct.

JS: But when you arrived, so at that time, Frank Young was the Commissioner of the Agency, I'm pretty sure, that was possibly, it was toward the end of his tenure, but he was still there. He was still the Director of the Center for Drugs.

MT: That's correct.

JS: And was Saul Sobel?

MT: Saul Sobel (Dr. Solomon Sobel) was the division Director for Metabolism and Endocrine Drugs. Okay. And at that time, we had two offices for drug review. One was headed by Dr. Bob Temple (Dr. Robert Temple) and the other was Jim Bilstad (Dr. James Bilstad).

JS: I see. So, as you arrived, what was your impression of this place and these people you were around before you had a chance to get into it?

MT: So, the first time I came here, I just came here to give a talk and there were no expectations. I just wanted to talk to people about what I did. I do not think I was nervous at all. I remember giving a talk about the work, and I also recall a lot of people asking me a lot of questions.

And I was just answering what I knew. And when I did not know, I said I did not know. But it was an interesting experience. And I did not make much of it because I came here to give a talk. I think I gave a good talk and I left. And as I mentioned, as I was leaving was when Dr. Pierce asked me this question and I left. I was like, yeah, if there is an opportunity, let me know and we will take it from there. And then it just followed that they sent me this letter offering me a visiting scientist position. So, I joined. And then, I remember the first day I showed up for work, they gave me a bunch of files about a foot high.

They said, “this is it, and here's a review that you can do.” And I just looked at the files and I looked at the package that I had to review. So, I went up to Dr. Pierce. I said, “can you give me an example of a previous review?”

JS: Was this your training?

MT: He gave me a review from a previous application. So, I took it, and then I just started doing the work. I started reading the submission. I started writing my comments, and I used the template that he gave me. The model that he gave me had a template. I followed the same template, and I did it. And the one thing I remember is in those days we did not have a computer.

I mean, we had people who would type our reviews. So, my first review, I wrote it by hand, and I gave it for typing. It came back, two weeks later or so. I do not even recall the exact time, but it came back considerably a few weeks later, and it had several mistakes on it, several things.

And I said, maybe they did not understand my handwriting. So, I corrected it and I sent it back. It came back again a few days later with newer edits. And those were times when you used carbon copy, carbon paper for typing. So, I figured out that this was not productive. I told Dr. Pierce that, "I wouldn't mind typing stuff on my own," although I didn't, I mean, I've done a little bit of typing training, but I'm not a good typist. So, they got me a Wang computer, the old one.

JS: And did most people, most reviewers have these?

MT: I do not remember. I think people, some of them I know were handwriting and sending it for typing. I chose to type my own. And because of that, I felt, now after several months or years, I figured out that I had an edge over some of the others because I was now turning around stuff at a much faster rate because I was doing my own typing and getting things done sooner.

JS: But was it your sense that other reviewers were facing similar problems in getting their material?

MT: I have never spoken to other people about it, so I do not know what was going on in their mind or their space. But I say it is Monday morning quarterbacking, right? And they are saying maybe that was why they felt I was doing a good job. Because I was turning things around faster. So, it got to a point where, all of a sudden I get a memo from Carl Peck, who you know, was the Center Director, saying that he wanted to meet me. And I was nervous and was like, why is this man wanting to meet me?

Because, those days, the Center Director was next to God, and Carl Peck for that matter was, if you've seen him, he would be somebody you could take straight out of a movie for that role, right? He was an admiral. So sharp. And I went to Carl Peck's office. I believe my meeting was at one o'clock and Carl Peck was late. I was waiting there. It was 1:30. And then at 1:40 he walks in and I am sitting there, nervous about what this conversation was and why he wanted to meet. And so, as you can imagine the time lag is just building up the agony and angst in me. And then Carl Peck walks in and he starts apologizing to me for being late.

He says, "I am so sorry. I knew our meeting was at one o'clock. I am so sorry." And I am like, I do not want you to be sorry. I just want to know why you want to see me. So, he said, "I just wanted to meet you because I have heard nice things about you. I heard you are doing a great job, and that is why I wanted to meet you and say hello and thank you." And I do not know what got into him. He just quickly said, "Is there anything I can do for you?"

I am somebody who does not miss an opportunity. I told him, I said, "Listen, I finished my medicine in India. I came here, I did work in Philadelphia as a research assistant and as a fellow in lipid disorders. I would like to get some additional training."

And he immediately picked up the phone and called Ray Woosley (Dr. Raymond Woosley) who was in Georgetown. And again, Ray Woosley, if you recall, was one of the top-notch clinical pharmacologists, even today, I believe, he is well known. At one time he was considered to be our commissioner.

I then was told to go and meet Dr. Ray Woosley. And basically at that time, again, it's all a matter of timing because apparently at that time, Carl Peck and Ray were talking about having an FDA fellow train at Georgetown and at FDA in clinical pharmacology. So, the timing was such that, he said this was a DIA-sponsored fellowship.

I went and met Ray and they said something to the effect of, 'Yeah, you have come right in here. We will do this and you'll do a fellowship.' And that also created an interesting turn of events because I was hired here by Division of Metabolism and Endocrine Drugs. But then all of a sudden in less than six months, they are now talking about sending me off for a fellowship. Or by the end of the year, the [Georgetown] fellowship was starting in July. So, I started [at FDA] in August [the previous year]. By next July I will be starting this fellowship. And I think DMEDP was not happy about it.

They went into Carl Peck, and said something like, "We hired this guy to do review work and you're sending him away." So, an arrangement was made that I could work part-time at FDA. I came in on Saturdays and sometimes on Sundays to do my review work. And full-time I was at Georgetown doing the fellowship part.

Now the fellowship included posting in the FDA. So, I did a part-fellowship period under Steve Fredd (Dr. Stephen Fredd) in Division of Blood and Guts, Gastroenterology and Hematology products. And I also did a part of my work in DSI [The Division of Scientific

Investigations in the Office of Compliance] at that time. I did that, and then I went back and I finished my fellowship and I came back to Division of Metabolism and Endocrine Drugs.

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JS: So, that's helpful to know how all of that unfolded because, I was kind of wondering, looking at your resume, how that worked. Stepping back a little bit to the division so you – obviously your primary interest was, was in lipid lowering drugs, but the division of course also handled obesity drugs.

MT: Yes.

JS: And you were there at a very interesting time in this, there are many, many products, but one that came under review, around the time you were there (and I don't know if you had any involvement with this, given your interest in lipid lowering) was dexfenfluramine, Redux, which had a very interesting history and a bit of a controversy.

Number one, I mean, did you have any sort of direct involvement in that whole maelstrom, if I may? And number two, even if you didn't, what was going on? This must have been a source of great discussion in the division.

MT: It was, and I was involved as a very first-line reviewer. It was a remarkably interesting time. Obviously the previous fenfluramine was marketed as a drug at that time for weight loss, but it had only been studied for a couple of weeks, if I remember right. It was a very short-term

study. And now there was an approach, I am just calling recalling at this point. I may not be totally accurate on all this, but I had actually placed it when, now when you brought it up, I just thought about it. And at that time, I remember recommending that if this has to be brought forward, I think there should be longer-term studies that need to be done. To determine its safety and efficacy.

But obviously because it was a product on the market already, for short term use, there [were] a lot of challenges. I think it was around that time that I switched from metabolism [to DSI], so I did not see the follow through and the end of all that. But my limited engagement was in looking at the initial, the dexfenfluramine application and asking that we get more safety data.

I do not recall what all went on in Metabolism and Endocrine Drugs later, but I know that the product eventually was approved, but then I believe it was taken out of the market because of safety concerns. So yeah. And there was quite a bit of drama, all that, I did not have any firsthand involvement.

JS: Right. But certainly not the first time that this sort of thing, that you were involved in. We'll get around to more.

MT: I think again, it was the hand of God that removed me away from that. So, again, I felt that it was good timing that I just slowly drifted and moved on to something else.

JS: So, when you were at Georgetown, did you work under Ray Woosley?

MT: Yes. I was reporting directly to Dr. Ray Woosley. And, since you brought up the anti-obesity issue, when I was in Medical College of Pennsylvania, I worked on a clinical study, for which David Capuzzi was the principal investigator. And I was one of his sub-investigators working on a lipid-altering drug.

But I went to work with Dr. Ray Woosley. I had the opportunity, again, to work as a sub-investigator on a potential anti-obesity drug. And it was a great experience. We were trying to determine the cardiotoxic effects of the product. And so, it was a genuinely nice experience to gain that experience from getting patients and trying to evaluate the cardiotoxic effects after dosing.

JS: Right. So, at Georgetown, among the things you were involved in, you were working as an investigative participant in phase-two studies, right? With a variety of drugs including - were you working with drugs that could eventually be, depending on their outcome, end up in the division for review? The reason I ask is, was there any sense of a conflict of interest? Really, in terms of somebody who's obviously involved in the investigation, and yet also has part responsibility.

MT: I think as part of the fellowship, the understanding was that if I ended up having to review any of that material, I would recuse myself, right? But as a sub-investigator, I was just doing the job for Dr. Woosley. And I did not feel any conflict of interest in just evaluating the cardiotoxic effects of the product.

And again, the studies that we conducted did not yield any substantive results, at that time, although later, that product, again, had enough toxicity that it had to be taken out.

JS: But it would seem to make sense. But the mindset behind setting this very fellowship up, in Dr. Peck's eyes, was a good idea to give viewers experience in what these, how these are carried out.

MT: Right. It was a valuable experience. I remember working on another project, which was determining the absorption of morphine that could be applied sublingually. It was another fantastic project that I feel so blessed to have had the opportunity for working on such small projects that gave me a lot of insight into the work that FDA did.

Initially as a reviewer, and later on when I moved into other areas in the FDA, it was all that experience was so valuable.

JS: Well, you had mentioned that part of this fellowship, you also served the Division of Hematology and Gastroenterology. You got blood and guts.

MT: Blood and guts. That is what we used to call it!

JS: Well, I love that. But one of the things you were doing there was, you were auditing clinical trials, and I'm wondering if this was, considering where your future path, was there some foreshadowing here of what you'd be doing?

MT: Not really. I mean, part of my work, I said, was with blood and guts, and [other] part was with DSI, and it was that DSI fellowship part that got me to go out on inspections with some of our veterans at that time.

If I may mention the names, maybe not need to mention the names, but they were veterans in DSI and I got to see how they did [inspections]. My role was just purely observing them. And I got to see how they went into a site, presented themselves, what they reviewed and how they were able to elicit information that is not just very apparent when you are reviewing an application.

That experience was so valuable. I did not think about joining DSI at that time. But again, going back to this narrative and the theme of this hand that guided me, I ended up having, when I came back after my fellowship, I was reviewing an application. It was a simple application, rather than getting into the product detail, but the biggest problem I uncovered was they did an entire study without knowing what dose they were administering. And I was stunned, that here you have a study with results and graphs and everything. But then when I called the company (those days, we could call the company directly). So, I called the company, and I said, “What dose did you administer?”

They said, “We think we gave this dose.” I said, “How did you figure that out? Because the vial that you gave had a lot more product in it.” And it was not a Metered-dose dispenser. I said,

"How did you figure out this dose?" And they went back and did some additional work and figured out that they could not specify what the dose was.

And, also at that time, through Metabolism and Endocrine Drugs, we asked DSI to do an inspection. And the DSI inspection came back and concluded with my finding that they did not characterize the dose. So that is when I figured it out, you know what? I could be sitting here and reviewing data. And my assumption is that all this is very factual.

But there is more to it. And I spoke to folks in DSI, and that time, Dr. Frances Kelsey, the legend of the thalidomide reviews and all that, she was there. And I expressed my interest to Dr. Kelsey and Dr. Lisook. I think my conversations were more with Dr. Lisook, saying, "I'm very interested in what you're doing." And they said, "Okay, we will take you on as a pharmacologist reviewer, scientific reviewer."

JS: Just one thing, one mile-post I wanted to pass before jumping into OSI, and that was another part of, you had spent several months during the fellowship with endocrine and metabolic during that time, in the division of epidemiology and surveillance. And I think you were focusing there on post-marketing surveillance and, one involving a non-steroidal anti-inflammatory drug that turned out to be, yet again, another one of these interesting products that FDA phases; in this case it was Felbatol.

MT: Yep.

JS: Now, is that something you were involved in? And if you could just maybe tell me a little bit about that experience.

MT: Yeah, I do not recall all the details. I remember working on, I think it was at that time, called Felbamate, I know it was, I did work on the initial review and collected the data and wrote up a summary for, I believe it was Dr. Friedman who was working at that time there. And I gave it to him. It was an interesting experience of collecting post-market surveillance information and putting it together. I do not recall the details of my review; unfortunately, last week I shredded that document because I am leaving now. I kept it with me. I saw it, I said, oh my goodness, I worked out this, but then it is not there for me to go and look at it anymore.

JS: But this was an anti-epileptic, right?

MT: It was, yeah. It was a pediatric concern. I believe it was being prescribed to children with epilepsy, if I remember. I do not recall the details, I am sorry, but I did work on it, and that was an interesting project I was doing.

JS: Eventually, it was withdrawn, from what I remember. I think that might have been later.

MT: Yeah. I have had the good fortune or bad fortune of working on several products that eventually had to get out of the market. So, there's tons of experiences that I can talk about.

JS: Good thing that we find out about these things, right? So obviously, as you started to describe, your next move was actually to the Division of Scientific Investigations. A pharmacologist and scientific reviewer, is that correct?

MT: That's correct. Throughout this journey in Metabolism and Endocrine Drugs, I told you I started as a visiting scientist and then I was a staff fellow. So, then I became a U.S. citizen, and then they converted me to a U.S. staff fellow. And I was continuing as a staff fellow, and that was not a permanent position. So, part of this experience of trying to move into epidemiology was in search of a permanent position. And then this opportunity in DSI came up.

And that was when I ended up with a permanent pharmacologist position. And that was that transition. And getting into that role got me a lot of interest in doing, looking at the quality and data integrity issues.

JS: Absolutely. I want to talk a little bit more about that, but you started to reference some of the almost legendary character scientists. Dr. Kelsey, and there aren't too many people still around at FDA that had the experience that you did of actually working under her. Dr. Alan Lisook. He had served in that division for almost for as long as Dr. Kelsey had at that point, I imagine.

What was that like? What was it like working under, particularly Dr. Kelsey, and, and what sort of impact did – what lessons did you learn from her that you carried forth into the rest of your time at FDA?

MT: Obviously, you know, what you are talking about. Dr. Kelsey and Dr. Lisook it fills me with a lot of emotions.

Dr. Kelsey, I believe, was about in her eighties when I was hired to work in DSI. And it was remarkable to see how a person like Dr. Kelsey was revered in the FDA. She was very well respected. And even within the office, people were very – nobody took chances with her. And if you sent a review to her, you better be accurate because if you are not accurate both in the way you write your English as well as the content, she would definitely come back to you and make you feel that you need to improve your stuff. And she had a way of communicating that, and I respected that.

I thought it was so - I always saw her with a sense of awe and learned a lot from her. And I remember her, I think I may have mentioned this earlier [before this interview], I once sent a note to our division folks for happy hour one evening. And she came back that evening and she said, I saw your happy hour invitation. I just want you to know I'm not running a "loosey-goosey" place.

JS: Does she think this was going to be on-site?

MT: And that was it. That was it. But I got the message. Dr. Alan Lisook was absolutely a phenomenal individual. He is so simple, so humble. And one thing he really taught me is how to evaluate information objectively. When I get a review, I would write my review and send it to him.

And again, those days, I do not think everybody used a computer. So, I would send him this written review [or printed review]. He would take a legal pad; he only wrote on the legal yellow sheet. So, he would take that 8 by 14 pad, and he would write every section that he wanted to reinterpret what I was trying to say.

And I would get that and read it. And I would say, "Man, what a beautiful way to say this, rather than all the confusion that I caused writing it." So that was a huge educational experience for me. And that his focus was so [objective], he would not worry about the person, the site, nothing else would bother him.

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He just taught me how to zero-in on the data and look at the data integrity issue. That was a very valuable lesson for me and, I really appreciate the opportunity for having worked with Dr. Kelsey, Dr. Lisook, Tony El-Hage, who was there; Gus Turner, Bob Young, Dr. Vishwanathan, all these guys were big in their area at that time.

Dr. Bett Barton, I am sorry, I forgot to mention her. So, all these people were such an inspiration. And that was not as big a team as what OSI is now, but it was a small team. It was well respected even within the agency. And I thought we did a lot of interesting, good work.

JS: Well, speaking to that good work, I know you're obviously closely involved in clinical investigation inspections. Most people don't know what these investigations consist of. And, we can go into great details later, but could you talk about what's entailed in a clinical investigation, what happens and what you might see? I'm sure you have some wonderful stories that maybe could be relayed in an anonymous way.

MT: Yeah. This clinical, first of all, the word investigations, clinical investigations, carries multiple meanings. In the regulation, a clinical investigation is when somebody does a clinical trial or a study. But that's different from what FDA does, when FDA conducts an investigation or an inspection. So, FDA's role, is we get a package, an application is submitted to the review division for a marketing application, or sometimes it might be for starting a new study in human beings under an ID.

And then a team of reviewers is reviewing it at the review division stage. And they would sometimes send a consult to DSI or the Division of Scientific Investigations, to look at the data and see if there's any concerns that an inspection would find. Now, that's when DSI would assign [an inspection] that obviously [identifies] a site [for inspection], a study may have anywhere from 10 sites or one study sometimes [may have up] to 5,000 sites sometimes, right. And so, we do not have the luxury of going and looking at everything. We have to figure out how to sample a few sites and look at the data there to see if we can extend our thinking to see if there is a systemic problem in the entire study.

So that is where we send out these assigned inspections. And the actual inspections, then are done by ORA, Office of Regulatory Affairs,. Field investigators. They're called investigators,

but they are FDA investigators. They conduct two things. Again, they conduct an FDA clinical inspection, or they can do an FDA investigation.

The investigation is when they just go and try to get the facts. It is more of a fact-finding thing, in some instances. But the inspection follows a certain protocol, we call them compliance programs, and they go through a very meticulous way of assessing how the study was put together. Who is in control? Who are the players involved? What they did, did they do what they say they did? Did they document the data properly? Was the data transferred from their site to the sponsor side? Was it done accurately? And again, did the sponsor package the information properly and submit it to the FDA?

And so, it is a chain of events that happens. And the goal of the inspection, the FDA inspection, is to see where the source of that data [was] generated and how it went through all that process in multiple hands and arrived at the FDA, and to see if it is the same information or if it has been altered in some way.

So that is one big part of the inspection. Now sometimes, because there is an incentive for investigators to do these studies, they could manipulate the data even at the source. They could generate data without an actual patient in there. Or they could try to take one patient's data and make it look like they were two different patients.

One could be Mathew Thomas, the other could be Thomas Mathew, and you could submit the information that way. There are people who are supposed to be doing the study [properly]. They could figure out, they could probably say that somebody else, John Swann did this entire study and captured all the data when John Swann was not even working for them, so those kinds of things happen and [fortunately] they're not often, but there are instances. Some of

these examples I mentioned [are incidents] that have happened, and that is where the role of a DSI inspection and the role of the FDA investigators [may help unravel the facts].

And in some of the inspections, we also from DSI, can go and participate. That is where we find out, wow. Did they really do what they said they were doing? Or is there something else to the story? And that is the fun part, so it's pretty much like doing an investigation in any other area where you have to unravel the actual things that happened and see if it doesn't make sense.

Most cases you will not [find much], [because] our inspections [are] very time constrained. We typically have only about a week to do this. But when we do this, the question is, are we looking at enough information to get a feeling that all this is good? In which case, we would say it's classified as an NAI inspection. We will say everything is okay, no action is indicated because we did not find anything. That does not mean there was nothing there, but the inspection didn't find anything.

Then we could have something called a VAI inspection where we do find things went wrong. But those are things that were errors or things that the investigator can voluntarily correct. So, we would talk about it, we would send them a letter and say [what we found]. But then there were instances where there is either deliberate falsification of information or repeated violations. Then we classify them as OAI inspections or what they're called “Objectional Action Indicated.”

And those, sorry, not objectional, they are objectionable violations. They are “Official Action Indicated.” And we then send a letter, either it could be a warning letter or if it is repeated or deliberate violations, it could even be escalated to a notice of initiation of disqualification

proceedings, and there's a lot of other things that follow from there. So, that's a gist of what DSI does.

JS: Does one tend to see more problems the more number of centers that are involved, or can you see as many problems with, depending on the number of patients, a single center?

MT: I do not know if we have seen problems with single centers. We have seen problems in multi-center study. It all depends on how – so part of this clinical trial process requires something called monitoring. The sponsors are supposed to monitor the progress of the study, and usually a failure of monitoring is what results in them [finding problems], the sponsors not catching these [problems].

Now there are a few instances where maybe they do catch it and they just ignore it or let it go. But, most cases, I think if a protocol is well written and if the study is well monitored, the chance of you finding problems is limited. The problem is when you have a protocol that is not properly written and includes a lot of steps that people either cannot do or don't want to do, and then you don't monitor the study adequately, so nobody is knowing what's happening as the study progresses, you figure out that a computer is not working where they're supposed to enter the data and somebody just ignores it, and then two months later everything is being entered, after a two-month delay. Those are things where monitoring should adequately document stuff.

There are instances where monitoring itself could be problematic, right? So, it is a process. It is a very well-prescribed process, and if that process is properly followed, you will

end up, whether it is a single-site study or a multi-site study, you should not have problems. And a clinical trial has so many variables.

Usually when you go to a site, you do expect to see problems. You do expect to see things that were done exactly the way they were supposed to be done. And that happens because you are dealing with different kinds of patients. They are traveling from various places. They may not show up on time, or maybe they had an illness, they could not come for a specific visit. They may have had a death in the family, all of that if it is properly documented, then when you are going back to reconstruct information, it is all there. The problem is when you go back to reconstruct, and the information is not there. They say they called the patient, but none of the patients have phone numbers, so how did you call them?

JS: So, the ORA Field Investigators would handle these, but sometimes staff from DSI Would go out on inspection. What would trigger having the staff go out on an inspection? Were, were these particularly complicated or something else?

MT: Obviously if I am assigning five inspections, I would not have the ability to do all the five inspections. And then if I am dealing with multiple applications, I would not be able to go for each of the applications.

So, the information the ORA field investigators collect for us has tremendous value. They do such a good job of going there and giving us the information, which is immensely valuable, particularly important. In some instances, we choose to go, because there is a large site, there is too many patients, and we feel that one additional hand to work with the [FDA} investigator would be extremely helpful.

There are instances where the review division may come and tell us, “We are not very sure about this data. It does not look good. Can you go and look at it?” Sometimes the information is more scientific and so we go there and say, “Okay, let's look at this information and see what's happening out here?” So that way, there is a lot of added additional scientific input somebody from the center can add [as a subject matter expert].

Also, if there is a large volume of work then the person going can help. I alluded to the fact that the investigators usually only have a very constrained amount of time to do one inspection. It is typically a week. It could be extended, but it is not common to extend it that way.

Especially the olden days. You could extend it sometimes indefinitely, but not anymore under the PDUFA you cannot. So, having an additional person would definitely be a big value.

JS: There must have been some truly notorious cases that the division encountered over the years and these individuals would have been disqualified. And there's a published list of disqualified investigators.

MT: That is right.

JS: Can you recall any that, that caused a particular amount time invested on the part of the Division and particularly those that might have been repeat offenders before they earned their name on the list of disqualified investigators?

MT: Again, in DSI I have had the good fortune, or misfortune, depending on how you want to classify it, of dealing with several OAI cases.

My first overseas inspection was an OAI case. And in that instance, I am not going to mention any names, but I can tell you the examples. In that instance, the [clinical] investigator was such a nice guy. He was such a simple, decent, nice person. At least that is my opinion. But he was doing this study in a foreign country and the sponsor at some point, sent a note to him saying, "Hey, we are arranging an investigator's meeting, and we want you all to come to this particular city."

So he went to that city, and they gave him them [all clinical investigators] new completed case report forms and said, "Take these and go replace your case report forms with these case report forms."

JS: These were completed case forms?

MT: Completed case report forms that this particular sponsor gave to the investigator. And then the funniest part was a few weeks or months later, I do not recall exactly right now, they sent another letter to him saying, "By the way, remember the meeting we had and we gave you those case [report] forms? Those are not right. We want you to discard those. And here is a new set that we are sending ."

JS: Oh my. Right.

MT: Now, the reason I felt this investigator was a nice guy is he did keep that memo on file, and I had a translator who was able to translate it and tell me exactly what happened. But it was an interesting experience.

I do not think I have run into a situation like that after that. But there were other investigators who have done all kinds of stuff. They create patients who do not exist. I know of one guy who actually saw two patients for a pelvic inflammatory disease [study]. He saw two women, but then he submitted data for, I believe, 27 or 28 women, in that study.

And the actual patients were patients of a doctor who was across the hall from him. So, unrelated to his study. His coordinator went there and took the charts of these women with pelvic inflammatory disease and made it look like these were his patients. They never consented. They did not even know they were in the study.

Right. So that is one example I recall. The same investigator had a study that he was doing. Now, these are all, these are all old cases, but, and some of this has been, some of it, not all of it has been actually reviewed and published in the New York Times. And I believe another case that I recall was published in the Washington Post.

So, going back to this case I was talking about, he had a nurse who had proteinuria. He would collect the nurse's urine and keep it in the fridge. And he actually paid her for her urine. And then for every patient who was required to have proteinuria at the time of enrollment, they would take a sample of her urine and substitute it for the patient.

Another study that this investigator did required patients with rheumatoid arthritis. So, he would take patients who were with no arthritis, take an x-ray from somebody who had arthritis,

put that as the appropriate initial x-ray, and then do another x-ray to say that they're all now doing well.

So that is one case that I could remember. The other one that I talked about in the Washington Post was, again, a foreign study where I did the inspection and they said that the IRB had reviewed the study and gave us the information. When we did not find anything, we just got it [the documentation of IRB approval] and came back.

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But the Washington Post investigator figured out that that IRB letter was actually signed by the clinical investigator's secretary saying that the IRB [reviewed and approved the study].… We could not go to this foreign country. So our inspection was very local in the U. S., but the Washington Post investigator found out that information.

There's another investigator that I can recall who actually FDA had inspected multiple times, and we always either found him NAI [or VAI]. He was supposed to be a good [clinical] investigator, quote unquote. And so good that I believe the agency (ORA) was actually inviting him to give talks for the FDA investigators as to how they do clinical trials.

And then, we got an informant, saying that he was doing studies inappropriately, and then we did an inspection. Then we expanded the inspection to involve OCI, the Office of Criminal Investigations. And we did find out that he was enrolling patients who were supposed to have bronchitis, and so they had to have a sputum that was positive for pathogen, but the sputum was actually being collected from two or three individuals who had bronchitis and were being substituted for people who didn't have any bronchitis. So, this particular case, it was very helpful - the sponsor actually worked with us. I remember the sponsor really did a DNA analysis and

found out that, I think, at least in about 20-21 cases, the sputum was collected from one individual.

And there were others. So that is the other case. There is another case that I could think of where the investigator actually claimed to have completed physical examinations and all that for patients when he was not even here in the country. He was overseas.

Now some of these things we ourselves would not be able to uncover. But later, what we do is when we get into an area where we suspect this level of fraud, we sometimes engage the Office of Criminal Investigations and they have a much greater ability to go and look for things that are beyond our purview. And so sometimes it is extremely helpful to refer the cases to them [OCI].

JS: So, they do assist with some of these investigators.

MT: They do not really, so our role is very administrative. DSI's role, or now OSI's role, is purely in the administrative area. When once the case is transferred to OCI, then they do deal with the criminal part of it. So, we do not cross that [line]. They deal with more mail fraud, wire fraud, all that kind of stuff. 18 U.S.C. violations. Ours is usually trying to deal with the code of federal regulation violations.

I may have given you a few, just a handful of examples, there were a lot more,

JS: I'm sure there are.

MT: I think at one point I had about 22 OAI cases, and that started wearing me out and that is when I decided I need to stop doing this and also look for a promotion.

JS: One other thing that you were very closely involved in DSI was in the development of their database of clinical investigators and I had no idea there were so many clinical investigators out there. So how did this come about and how does it, if you wouldn't mind just speaking a little bit to it, how it helps FDA do its job in overseeing clinical investigations?

MT: Again, I joined the agency [in 1989], I joined DSI in '95. A lot of things were done manually. We used to have one CSO, her name was Carolanne Currier, and just before we did an inspection, we had to go and tell Carolanne to pull us the data on investigator [e.g.,] Mathew Thomas. And so, she would go and she had a formula that she would write up and search the database and get us the information of whatever information was there.

So, it was very dependent on Carolanne's availability to pull out the information. She was fantastic. It was good. But, again, it happened that around I believe 2002 or 2003, our division director in one of the division meetings mentioned that there's a certain pot of money that they needed to use and, asked people if they could come up with some idea of using that money in a very useful way. And I just remembered I went and took a piece of paper, and I wrote a proposal. It was just two pages. I said, what if we can make the search electronic? And also, it's not only for use within DSI. Carolanne also spent a lot of time searching for information that was in response to FOIA requests. So, the Freedom of Information Act requests, right?

So, based on that FOIA request, we could minimize the amount of response time if people could actually [obtain most of the information] that were freely available [online] and [not] ask for a FOIA If they could access it on their own. So that is why I wrote up this proposal. And we came up with, at that time, a contract and as a database that was eventually created called the Bioresearch Monitoring Information Systems, BMIS. And it is a database that is now publicly available.

It is updated every quarter, with information on investigators who have submitted an IND, to the FDA. So, you can go in and type a name, [e.g.] Mathew Thomas, and then you can look in and say that, oh, Mathew Thomas has submitted only one IND or he has submitted 25 INDs. Now, the IND numbers are not disclosed because they are private [confidential and/or commercial] information.

I mean, they are confidential information, but you will see a date and each date represents that there was a submission for that person. So that is one way that the industry can also [know], if before they hire a clinical investigator, [they] go in and look and say, oh, okay, this is of a large-volume investigator. Could be good, could be problematic.

Or it is somebody who has just started doing studies that maybe less volume of work so they can do stuff. They can look that up. Also, as an extension of that BMIS database, we also started putting something [a database] called the clinical investigator inspection list [CLIIL], which then would say, okay, Mathew Thomas was inspected by FDA, on this date or five times before, and the outcomes were NAI or OAI – and we also used to include the deficiency codes as to what kind of violations they were. So, we automated that [process]. It was a database that already existed, but we started pulling information from that database [electronically] that could now be publicly displayed.

JS: The field organization, has gone through some permutations of the databases – of their inspection work. I mean across the board, right? But this was entirely different. This was just specifically on the clinical investigators.

MT: Yes, yes. So this work that I mentioned, the BMIS and the creation of the CLIIL I think happened somewhere, CLIIL, the Clinical Investigator Inspection List. These two databases, I believe, came into being somewhere between 2003 and 2005. That is when I think I was working on these things.

Now, the database you mentioned about, the Office of the Field Investigation, they have now a database called the FDA Data Dashboard, which is publicly available information. And it is an excellent database. It started populating information since October 1 of 2008, as part of a transparency initiative that I guess Congress wanted ORA to initiate.

So now, as of this year, we are finding that maybe we don't need to have these two databases, the CLIIL and the FDA Data Dashboard. But we are still thinking about what to do with it. We haven't, but most of the information you find in the CLIIL may also be in the Data Dashboard.

And one more point about that. The FDA Data Dashboard is not limited to just CDER inspections. CLIIL is only the CDER [GCP] inspections. The FDA Data Dashboard includes all the inspections that ORA does.

JS: So very busy times in DSI, but you made a move. [Recording paused.]

JS: Well, again, so much going on in the Division of Scientific Investigations, but you did make a move next, and that was to the Office of Orphan Products Development. That was from 2007 to 2011. You were a health science administrator. I guess my first question is, what led to this? Why Orphan Drugs?

MT: Two things. One was, as I mentioned, I was getting overwhelmed with the number of OAI cases. Once you get an OAI case, it never leaves you because it takes a while for it to settle down and for the final action to be taken. And then in that process, you got to explain the story over and over again to so many people on the chain of command. So, it is exhausting. At that point I was thinking, gosh, I need a break. Part of my problems were eased with my getting involvement in the development of the database and other things that I was engaged in in DSI. So, it did give me a break from just doing the inspections.

And the other reason was I also was looking for a promotion, and I felt that DSI didn't have that space for me to get promoted. An opportunity came up in Orphan Drugs, and so I interviewed and they picked me to work in Office of Orphan Products Development. We call them the orphans or the orphanage.

And I thought that was fantastic, again, another phenomenal experience of working in the orphanage, particularly because I felt that of all the places I've worked in, the Orphan Products Development Division or Office as it is now, is a place where you really work with sponsors to

develop products for rare diseases, so you actually are offering them protocol assistance and giving them ideas of how to develop a product.

It is not a purely regulatory role, if you understand what I am saying. The DSI role is very much where you go and find problems or you come and say, there's no problem. On the other hand, in Orphan Drugs, you have a more positive role in working with them saying, “Hey, here's a need and let's figure it out, we can push for this thing and this may be something that we can do as long as it meets the regulatory requirements.”

JS: And this was also an element, an outcome of the 1983 Orphan Act, right? After they encourage the facilitating, the attention to the needs of rare diseases.

MT: I am a big admirer of that 1983 act. I think it has enabled so many good products to come on to the market, especially for the populations that are small for which the companies are not going to invest money to do their studies. So, for rare diseases, it is really a helpful act that enables that.

JS: And currently there are quite a number of drugs that have received that designation, right?

MT: That's correct, yes. There are a lot of designation requests that keep coming. As is always the case, people look for small loopholes here and there to get a designation and do something.

But I think for the most part, the Orphan Drugs division, the office, is careful in how they designate products, and also very meticulous in how the grants are being given for people who want to do studies. And also, now with our collaboration activities with Europe and other regulatory agencies, there's a lot more collective thinking on how to facilitate the process.

JS: So how does the agency handle requests like this? What does one look at? There must be a number of factors that enter into whether or not they can receive the designation, right?

MT: Designation requests are mostly sponsors figuring out that this is a need, an unmet need as a small population.

Let us come to the agency and ask for a designation request. Because once they get a designation, they have certain incentives, they get tax breaks. They, I believe they have a lesser, or they waived the PDUFA fees. I do not know exactly what that is, but I know there is some fee reductions maybe, I don't recall that right now, but definitely they do have tax incentives for doing their studies. And that is a huge benefit for them.

And also for certain designations, they can also get priority vouchers; for example, if they're developing a product for tropical disease, treatments or for pediatric populations there are vouchers that you can get, that the companies can actually sell to somebody else where they would get a standard review now bumped up to a priority review. So, they get an advantage of time. There are different pathways. I may not be describing them exactly the way they ought to be described, but that is the designation part.

With regards to grants, there is a time when a request for proposals is published and then based on that, people do submit applications saying that "Hey, we have interest in doing such study." And then those grant applications are reviewed, they are interviewed, they go through the process, and then the grants that are to be funded are selected and grants are awarded and then they're given periodic evaluations.

In the olden days when I was in Orphan Products, we used to do site visits where we could go to the site and actually see what they're doing based on the grant application and see if they needed some assistance and help them how to do it.

So, I actually developed a site visit template at that time that we could use. I gather we are not doing that many site visits on site, but we do that over the phone now because it is getting more difficult to go to the actual sites, I think, so most of those site visits evaluations are done by phone.

JS: How many grants are we funding? But also, does the funding come from some kind of separate source, or is this just pulled out of FDA's budget?

MT: I think it is pulled out of - I am not very sure about that, and I do not have the exact numbers. If you want, I can find it.

JS: No, that's okay. Yeah, just curious.

MT: When I was in Orphan Drugs, I had all this in my head, I moved on.

JS: This been a while ago, too.

MT: So, I don't have the exact – I remember doing so many talks for Orphan Drugs, and I used to rattle this off, but now I got to go and refresh my memory.

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JS: I'm sure what, whatever it was, I'm sure in the scheme of things, there was never enough money to give all the deserving applications, the monies they were asking for, though, right?

MT: Yes. But, and again, going back to the work at Office of Orphan Products Development, I personally thought that was such a fantastic opportunity. I really cherished that opportunity and I enjoyed it until a time when the office that I had left, DSI or OSI, was now getting engaged in outreach and collaborations with Europe. And so, I was asked if I had interest in doing that. And because I'd alluded that even in the Orphan Drug space, we were interacting with Europe a bit for doing that kind of collaborative work, so that got me interested in going back to OSI (I believe it was DSI at that point, but very soon after I went, it became OSI). And I was the Team Lead for outreach and collaborations there for a couple of years.

JS: I want to ask about that, because that must have been fascinating. Before I do, just one more thing I wanted to go back on. While you were in OOPD, you did spend time as a chair or co-

chair of the agency's IRB. And it made me wonder, you gotta look at either work that FDA itself was doing, involving human subjects or work, I assume, work that it was contracting for.

People probably have no idea the kind of research like this that FDA's involved in. Can you speak to your - this was for about a year. So, tell us a little bit about that experience.

MT: First again, I want to go back to that theme of some hand or force driving me from one thing to the other. So as you mentioned, I was in Orphan Products from 2007 till about 2011 and I believe early or late in 2008, I was approached and asked if I would chair the IRB, which was then called the RIHSC Committee, the Research in Human Subjects Committee, RIHSC.

So, because of my DSI work and familiarity with IRB requirements and all that, I said, "Sure, I'll do it." I ended up doing it for a year, for the entire year in 2009 I was the RIHSC Chair, and that was when I figured out that FDA does a lot of research. It is an amazing amount of research that FDA does, internally.

There's also a lot of research that is done by our Center for Toxicology and Research, NCTR, National Center for Toxicology and Research. So, there is all this research that we do that has to be reviewed. And if I recall at that time, the IRB I chaired had about 27 members. And I was told before I took this job that it is a very contentious discussion that evolves [during RIHSC meetings].

Fortunately, I remember taking on this role and I was a bit nervous about it, but I did set some ground rules and a few basic ground rules that I recall are, one is that everybody is equal when we are sitting around the table, and everybody should have an opportunity to speak and at

the end of the discussion, we will take the majority opinion and move forward, even if there are disagreements, we will make note of it, but we'll go with the majority.

I think the ground rules kind of established a confidence in people that everybody is going to have a chance to talk. I do not recall a single incident during that year where I had to struggle with any issue because, all the issues, everybody would talk, express, they would come well prepared, and it was smooth sailing. It was a great opportunity to review the work. There were some expedited reviews that I had to sign off and then inform the IRB, the risk committee. I had great support--I do not know if Suzy Fitzpatrick used to be the administrator at that time. The way I got enrolled into this role is I was doing a talk for DSI and Suzy was in the audience, and she went to Norris Alderson, who was then here and told Norris, this is the guy who can chair the IRB. And Norris Alderson is the one who came in and called me and asked me to fill that role. It was a role that I was doing in addition to my work in Office of Orphan Products. An important fact was let out here.

When I was the IRB Chair, FDA/CDER/DSI sent an assignment to inspect the FDA IRB/RIHSC activities. I am not sure if DSI had ever done this before. One morning, I show up for work and I have an ORA investigator issuing a Form FDA 482 (Notice of Inspection). I was initially furious and suspected someone was out there trying to get me in trouble. But then, I relaxed and cooperated with the ORA investigator to complete the inspection. The inspection concluded after a week and was classified NAI. So, I am perhaps the only FDA employee (as FDA RIHSC Chair) to have been inspected by FDA.

And now that you made me recall that role, I also got into another interesting role when I was in Orphan Products. And that was, Congress had asked FDA to submit a report on rare diseases. This was in 2010 or 11. I do not recall the dates, but they had hired somebody to be the

executive secretary for that. And that person quit, I believe, quit the role within a week or two, and then they hired someone else who was doing that role till November of that year. I should be better with these dates, but I think it was 2010, 2011. So somewhere around November 2010, that person quit. This report was due, I believe, in April of that year [2011]. April or March of that year - of the next year. The following year is 2011. And so, I had to step in in November of 2010. Again, don't quote me accurately on the date, whether it is, I think it is 2010

So, I got into that role and we, at that time, had a draft report that was several pages long. It was 84 pages or something, 84, 94 pages. And OMB came back and said, “That report cannot be more than 10 pages or 15 pages.”

And this executive secretary's role was to deal with all the centers, CDER, CBER, CDRH and all that, and all these big guns were at the table wanting their piece in that report. So, for me it was an interesting experience of trying to negotiate with all the big guns. And we did eventually submit a 15-page report or something. And what we did is, everything everybody else wanted to say was put in the appendices and the report itself was narrowed out to a short report. So it was a very interesting process where I was able to work with a lot of people and get something to Congress by the timeline, the way they wanted it with everybody walking off saying, “Okay, my piece is in there,” but it's just…it was a very creative experience and I felt very proud about it because I just got into that role and I felt, wow, this is a nice, great experience.

It was signed by Peggy Hamburg [Margaret Hamburg]. It was a report that commissioner Peggy Hamburg had to submit. So again, it was one of those documents I shredded last week.

JS: Well, fortunately, that's in the record.

MT: But my name is not there because obviously you do not get anybody's name on that report to Congress, but I felt very good working on it.

JS: It's a memorable experience. So, you had started to talk about your return to the, I'll call it the Office of Scientific Investigations. As you said, there might be a period there where it was still DSI, but obviously you get very involved in BIMO, the Bioresearch Monitoring inspections, not just any but working with international regulators. Now, that must have been interesting, and I imagine there were a variety of logistical and a variety of challenges working with other regulators who were, obviously, proceeding on the basis of their own statutes. Not our stuff. How did that work? What was the collaborative process like in this assignment?

MT: So, my taking on this role was in 2011, I believe. And by then, some preliminary work had already been done in OSI. I think this initiative for interacting started somewhere in 2008 or preceded my time. So there was some groundwork that was already done, some MOUs that were developed, so by the time I got on board, it was just a matter of setting up regular meetings, and exchanging information on a periodic basis, and then trying to figure out how to make this process more efficient of exchanging information.

So those days, again, we had to – because of the requirements for protecting confidentiality and trade secrets, we had to redact a lot of information, so redaction was a big

process before we could exchange information. I think now we have come beyond that a bit where we can exchange information a bit more openly, and then keeping track of all the applications that have been submitted to us, to them, and exchanging whatever information we have based on inspections and findings on a periodic basis.

Over time that started building up. So again, I created a template of how we could keep track of this information over a few sheets of paper. And I think that template, to a good extent, is still being used to keep track of all the information. Those meetings still happen. I think now they are more on a monthly basis or maybe even biweekly, I don't know. But those meetings are still continuing. It was a great [regulatory] process with Europe, and MHRA. MHRA is the Medicines Healthcare products Regulatory Agency in UK. They used to be a part of the EMA (European Medicines Agency), but with Brexit, they separated. Now they are on their own. EMA is the rest of the countries of the European Union. When I was involved, MHRA was a part of EMA. So, it was easy.

And, their inspections, I've observed some of their inspections. They pretty much do most of the stuff we do, except they did have a few different approaches. I don't know how they do it now, but those days, when we would go for an inspection, we would give them a notice of inspection, which is called a Form [FDA] 482 for domestic inspections.

JS: Is this a notice of advance -?

MT: No, no. This is when we go to the site. At the site. And then at the end of the inspection, we give something called a notice of inspection findings, which is a Form FDA 483. They do not

have those processes. They do not give a notice at site or at the end of the inspection. They do collect advance information, in advance of an inspection. At that time, we never used to do that, but now we are also in a process where we do collect advance information.

JS: Are they aware of that? I mean, is the place that's being inspected, are they aware that information is being collected in advance or is this just done without their knowledge?

MT: Now? I think because of COVID and because of our new approaches of doing remote inspections, there are processes in place and guidance where we do publicly say that we can collect information and do that.

So, not in all cases, I believe, but in some cases, we can collect information in advance. And, again, at the end of the inspection, they do not issue a 483. We do. They go back and discuss their findings and then send a letter basically saying what their findings are, and they categorize their findings as is a minor, major and critical, instead of our NAI/VAI/OAI which actually to some [extent], I think, does make better sense because they're either minor findings, they're major findings or they're critical findings. So those are some of the differences in the processes. But otherwise, I think, their process works quite well.

JS: Did they observe our work?

MT: Yes. They used to come and observe our work. I don't know how it is done now, but those days when I was working, they always sent two people for an inspection. They never sent a person alone. So, it would be two people from two different countries, and they would come and do the inspection. Another difference that I thought existed, I do not know how it is now, is that the companies would actually pay for their travel. It is not the regulatory agency [that paid for the EMA inspectors]. The companies would pay for them to do the inspection. So again, I do not know if that is still in play or not. And because of that, I think some of them used to fly business class or first class.

JS: I don't think that would happen in FDA, would it?

MT: I think even our Commissioner is required to go economy class, which I think is [not right], and then they have to pay extra to bump themselves up to business class.

JS: But it's a system that remains very much in place.

MT: Yes, this collaborative work is in place and is actually getting better, I believe, because I think if the same application is coming to them and to us, and if they're looking at three sites and we are looking at three sites, now we have information from six sites. And then if we do find a problem in one site, or they do find a problem in one site, then we have the information that we

can go and further investigate and figure out what to do. So, there is a lot more information that is now [avail]able, we can collect.

JS: The information that would be developed by another regulator, is that something that we could actually use and draw from moving forward in a regulatory position, or would that be acceptable or not?

MT: I do not think we can take regulatory actions based on someone else's findings. But if someone goes and says, "Hey, we inspected and there's no problem with this site," there is nothing. We can say, "Okay, we accept your results."

But if they find a problem, then I think it may demand our reinspecting the information and getting our own findings.

JS: You had a detail, after OSI to the Center for Tobacco Products, which was our newest center, and they obviously come from a different law that was launched under the Tobacco Control Act of 2009. I know you weren't there a terribly long time, but, I did want to ask just a couple questions about that experience and so, from your observations - and there, I believe you were based in the Office of Compliance and Enforcement, is that's correct?

MT: That's correct.

JS: So how effectively did you think CTP had embraced its regulatory role at the time you were there? And what, based on what you had observed, what struck you as the center's most important needs, when you were there?

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MT: My time at CTP was short, relatively short in the sense that I believe I was there for only about five months. Maybe six months at most. I think it was less than six months. And I did not have much of a time to grasp everything that CTP was doing, and my moving there was not on a detail. I actually went there on a promotion. I was selected as a branch chief in their division of enforcement. I went there, but I didn't find [it comfortable]. My comfort level was not that great, to a point where I felt that - it was not really - my role was not very clear. I was not able to get a sound footing on what I was supposed to do and bring forth. And that made me – [leave] so early on. I kind of figured out I'm not going be here for long.

I started looking elsewhere and OSI asked me, hey, there's a position for director of, I believe at that point, it was compliance evaluation, but it eventually was formed into the Division of Enforcement and Post-market Safety. So, because of that promotion that I had as a branch chief, I applied for this role of Director for Division of Enforcement and Post-market Safety. And I came right back to OSI.

JS: Right. And as part of that, you were overseeing REMS. What's the acronym stand for?

MT: The Risk Evaluation and Mitigation Strategy . And I was also overseeing the PADE program, which is the Post-Market Adverse Drug Experience Evaluation program and the Human Subject Protection program, HSP. So those three branches – I had oversight over those three branches.

And it was the time when that office was literally stood-up, so, because of the reorg[anization]. So, I had a great time working with a team of folks and building up the office and a wonderful experience.

JS: I should ask, so under the REMS requirement – companies have to follow up an approval decision with post-marketing studies, right? But I gather it hasn't always been effectively abided by, by some firms. So, what kind of a problem has this been and how can the FDA kind of compel a firm to kind of pay a little bit more attention to that?

MT: Industry is always smart. They always find a way around systems. They work with the agency, they come up with the regulations and then they know how to work around it too. So, REMS has been something with which we have struggled. The Risk Evaluation and Mitigation Strategy program is a great program because sometimes we don't have all the information before a product launches into market, especially if there is a need, an unmet need.

So, after the product launches onto the market, a program to evaluate the risks and mitigate the risks is a fantastic program. Now, one of the problems is that, I think what you are alluding to is that if there is a new company that is now trying to develop a product, and they want to use a product that's under REMS as their comparator, sometimes the [original] company

may not be willing to share that information because they're under a REMS so they're still evaluating their own information.

I think there have been some issues with that, but I personally have not run into those issues. I was more involved in managing the office and getting together a bunch of people who could run the office really well. So, it was a great experience. I think I did that for about a year plus.

JS: Well, I certainly want to talk to you about your experience in India. This was a big change to what you've been doing in your career so far. First of all, how did this come about? How did this change in your trajectory at FDA take this big turn?

MT: Again, going back to my theme, I guess it was a hand that guided me there. I had the opportunity to go there in early 2015. And my visit was to actually, I don't know if the correct word is supplement or to just parallel the visit of our Deputy Commissioner at that time, the Deputy Commissioner was visiting FDA India office.

And we had had some leadership challenges in India, and the person who was leading at that time was just going [traveling] back and forth. So, they wanted somebody at the station, at the post for a certain period of time. I actually went there on a detail for four months. And I went there, and my visit coincided with the Deputy Commissioner's visit.

JS: Sorry, may I ask, do you recall who the deputy commissioner was?

MT: It was Howard Sklamberg. Howard Sklamberg was visiting and because of our visits, I mean my going there, I went there I believe, mid-February of 2015. And then soon thereafter, by March, the Deputy Commissioner was visiting. So, within a matter of a month, I just soaked in all the information happening in India because I was able to see the briefing package that we had, prepared for the Deputy Commissioner.

And that had so much information about all the stuff that was going on there. And then the subsequent meetings we had with the various entities over that, I think it was one week or two weeks, it was like a bootcamp for me. Within a week and ten days, I knew pretty much everything [that I needed to know]; I met all the people I needed to meet in India and I was all set. So that was a phenomenal opportunity.

And when I was there, I also figured out that the India Office was struggling to – the office itself with personal issues and there were not too many personnel there at that time. So, some of the local employees there saw me, and they liked me. They asked me, "Sir, can you stay on?" I said, "I don't make that decision." I said, "FDA headquarters makes that decision." But I basically expressed my willingness to stay on if they [HQ] selected me. So, they put in an announcement and they went through the process of selection, and then I was awarded the position to stay on.

JS: If I can back up just a little bit and we're talking about the India office. I might be way wrong here, but I thought it was in 2009, around the same month, there were two offices opened in India, right? There was one in Mumbai and then one in New Delhi.

MT: That's correct.

JS: So by the time you arrived there, was that still the case or had the - Mumbai had closed by then?

MT: I do not know how much detail I can discuss.

JS: Well, I know this well. This is just the facts.

MT: Actually, three offices were approved in India.

JS: Where was the third?

MT: The third one was supposed to be in Hyderabad. So, there was an office approved in Delhi, in Mumbai, and then Hyderabad.

Over the course of my tenure there, I found it quite challenging to oversee the activities in the Mumbai office. And I felt that logistically it would be much easier and pretty much cost effective for us to run the office out of one point in India, because whether you were in Mumbai

or whether you were in New Delhi, you still needed to travel from point A to point B to do an inspection.

You still needed to get all the things done. And it is much easier if you are at one point, rather than having… the [dis]advantage of being in multiple places. At that time [in 2009], I think, people did envision that it's much better to collect the information from these local offices. But I figured out that we could collect the information from New Delhi itself – was really not a huge advantage having these satellite offices. And my boss at that time was also of the same thinking and mindset.

JS: I'm sorry, just for clarification. You referred to a satellite, was Mumbai a satellite office?

MT: Yes. So, the director for the India office was located in New Delhi, and in the U.S. Embassy is in New Delhi. We [U.S.A.] have consular offices in Mumbai, in Chennai, in Hyderabad. I believe there are other places. There are consulates, they are run by Consul Generals. They all report to the Embassy, the Ambassador in New Delhi. Right. So, when you say there is a Mumbai office, there is no separate director. The director is writing, directing from New Delhi. And the supervisor is also in New Delhi. So having these staff, there in Mumbai I felt, was not a very efficient way to run the place, although I am pretty sure that people are going to disagree with that.

And my supervisor at that time, Lou Valdez, she was also at the same mindset. She felt that this was not very efficient. And the other thing is, no matter what, whether you are in

Mumbai or in Delhi or in any other place, you still had to bring in an employee. You had to get the clearance from the Ministry of External Affairs in India.

Right? So that itself was a challenge. So, it was much easier to tell them we are bringing everybody here to New Delhi and doing it [FDA work]. So I had to negotiate a lot of those kinds of discussions with the Ministry of External Affairs in Delhi, [within] the Government of India, so that we can reassign those posts to New Delhi. And we worked it out, so it was easier.

JS: Did the embassy have a role in making these arrangements, or is this something that -?

MT: The U.S. Embassy?

JS: Yes

MT: The U.S. Embassy was informed about it because obviously we have to worry about the space of where we put everybody, and also take care of their housing and all the other requirements. So, the embassy did have a role, but the Ambassador and the Deputy Chief of Mission were supportive. And they felt that it made more sense. The Consul Generals in Mumbai was – maybe they were not that happy because a part of their team is now leaving from there, but they were okay with the decision.

JS: How did the staff in Mumbai react?

MT: So again, I told you we had hiring challenges. There was only one person who was a full-time U.S. employee in Mumbai at that time. And that person's tenure was coming to an end. And then there were two locally employed staff. So, the two locally employed staff figured out other positions and they moved on.

The person who was in Mumbai at that time, since that term was ending, came back to the U.S. but then I think we rehired that person to come back and is still in Delhi. So, because of the situation, it was not as challenging as it could be otherwise.

And then even in New Delhi, the number of people at that time was small. So, it was a place where our office hired a lot of new folks to come in and work in India.

JS: What was the sort of optimal staffing level for the office between locally employed staff and FDA-based staff?

MT: From my time in OIP (Office of International Programs), which now is OGPS (Office of Global Policy and Strategy), we were told that we don't have a fixed number. So, the optimal level of staff is you have staff who are well trained to do the work that is needed. We usually, I may not give you numbers, but we need people who are ready to go out and do inspections.

So, they're typically people who have been in ORA and who have done inspections. We need people who are trained in doing manufacturing inspections, GCP (Good Clinical Practices)

inspections, as well as food inspections. And some of them do device inspections. And also, a lot of BIMO inspections that happen in India.

So, there is a bunch of people with these training that come in. And also, in addition to that, we have what we call Policy Analysts, and they're the people who are also at the front line talking with the Government of India, understanding their policy and regulatory policies. We also tried to collect information from the industry in India. We try to gather information from what is publicly available in the news media. So that builds our intelligence capabilities. And then together, the Policy Analysts put all this together and present data for us to figure out how to strategically work.

JS: So that, going to the issue of the role of the office in gathering information or intelligence, particularly about the commodities that are going to be eventually winding their way to the U.S. I know this was an important role of the office from the very beginning, right? Speaking to when you were heading the office, number one, how did you go about collecting the information, and how frequently was it conveyed to headquarters on a regular basis? And did you get any guidance from headquarters as to the type of information they were wanting to get? Because this seems to be one of the really important roles of the office.

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MT: And it is the one of the biggest challenges of that role. My background, being from India, growing up in India till I was 26 years old, gave me a good idea of India's political landscape as well as its geographical landscape. So, I knew where every state was, I knew what the languages were, I knew the people and to some extent the culture. And it is a diverse country. It's not like

you talk about the U.S., you have all these states in U.S., but it's a lot more homogeneous than what India is. So that understanding was beneficial at the very outset.

And then understanding how the regulatory system works in India is also important because it is not the way things happen in the U.S. Here, FDA's policies are pretty much well accepted throughout all the states. Everybody just does what FDA wants, right?

But that is not the case in India. The individual states have their own FDAs, so there's a Gujarat FDA, there is a different, Maharashtra FDA, they have these individual state FDA offices that have very different roles, and different focuses, depending on what industry is in their backyard, right?

The guys in Kerala may be more involved in foods and fisheries as opposed to the guys in Maharashtra or more focused on the manufacturing plant areas, so there is all these different focus areas that they have. And the inspections they do are also different. Most of their inspections are inspections of pharmacies. The manufacturing inspections have only evolved after them probably seeing what we do. And there's all these differences that you need to understand, and a big challenge is to communicate that information to folks here at the FDA because we think of every FDA and every part of the world operating the same way that we operate.

And it is not the case. I have never been to China , but I am sure that Chinese FDA operates in a totally different way. So, communicating that [back to our colleagues working stateside at U.S. FDA offices] is one of the challenges. However, the biggest advantage that we have had is folks here in the center sometimes tell us what they are looking for, and when we

know that, then it is easier for us to go and get that information and pass it on. The other big part of that role is to work very closely with the Government of India folks. And I was fortunate to have folks representing the Government of India who were very collaborative and cooperative with me. And the main reason for that was I was able to build a level of trust with them.

And I was very clear up from the very front [start] that I was there to represent the United States of America, but I told him [the DCGI (Drugs Controller General of India)] that I will work with you and tell you whatever I think is beneficial for you – the Government of India; you don't have to listen to a thing. But I will be very honest in my dealings.

And I think that set us off on a very good level of trust, to a point that many of the decisions that the Government of India made, they did consult me and, they did talk to me and I was able to give my opinion, not that they had to listen to anything I said, but I think they valued a lot of what I contributed.

There are specific examples that I 'do not want to elaborate on at this point, but 'there are a lot of useful things that we did for the government of India.

JS: So, did you also have to develop these liaisons with the state governments that you mentioned before? And was there anything like an AFDO, Association of Food and Drug Officials, that existed in India that kind of worked with all of this?

MT: Yes. I am glad you brought that up. Yes. So, part of my effort as I grew into that job was to establish a more direct relationship with some of the state FDAs, which obviously the central, the

federal FDA, was not very happy about because obviously, they're now thinking that you (U.S. FDA) are going to establish these individual relationships with the states.

I had to negotiate that to some extent, to say that, hey, you folks 'do not have control over it. What if we do this in such a way that we can together have some say in 'what is going on? And that, I think, appealed to them. And they started working [collaborating] with us on that. So, we were able to establish some individual [tripartite] relationships with the state FDAs.

And that was beneficial. Greatly beneficial. We could do that. And again, in India we had to not only focus on the drugs, because for drugs - India is considered to be a big drug supplier, especially in the generic drug industry. But foods too, and particularly seafood, India is a big supplier, and devices to a much lesser extent. Vaccines, a big extent. So, there are a lot of areas that we could work on together. And I think one of our major contributions was that we developed some training programs, that they would send their state representatives to attend. So, we figured out that disseminating the uniform information across states is something, is one way that they could go back to the states and make the playing field a lot more level.

JS: Pardon my confusion here, which I'm just trying to clarify for myself, but the India National Government has their own cadre, their own force of inspectors that go out and carry out that responsibility, correct?

MT: Yeah. But it is much less than what you think it is. As far as I remember, here maybe I can throw out a number, just not the precise number, but as an example. When I was there, I think the

central FDA had about a staff of about 650 plus people, maybe 700, make it a thousand, I don't know.

But that is serving a population of 1.2 billion at that time. Now, I think it's 1.3 billion or 1.34 billion, whatever it is, as opposed to us having about 18,000 FDA employees spread all over the country. We have a CDER that is 5,000 plus more, more than 5,000 people, I guess. So that is for a population that is 325 million or 340 million.

So, that's the kind of idea that you need to get of what the central FDA in India, the central FDA is called the CDSCO, it's called the Central Drugs Standard Control Organization. Some people call it CDSCO. Some call [pronounce] it CDESCO. So, they are the central party. The other state FDAs are Gujarat FDA or Maharashtra FDA or whatever.

JS: It seems to speak, what you're saying though, seems to speak to the importance of actually making this outreach to the state organizations as you were discussing.

MT: It is important. And again, my understanding, and I think now people understand that you do not have to reach out to all the states in the same way, because some of the states are not doing anything that is important for us.

There were the pockets for manufacturing, the pockets for seafood, the pockets for spices, they are all very dense and clearly identified. You do not have to go all over the country to do this. If you are doing it all over the country, you are just wasting resources. You can just focus on states that really matter and get the best output that you want.

JS: Speaking of inspections, the decision making about where to inspect, now that's what I'd be interested to talk about. assume that ORA and the centers have ideas of what should be inspected, but the India office personnel are on site. And so, to what extent did the headquarters here rely on the office to make decisions about, for example, which establishments to go and inspect?

MT: Most of the inspections that we do in India are directed from here [in the U.S.]. Headquarters will say, we have an application from this info, or we have a product that is manufactured in this facility, we are going to send over ORA to inspect and to a good extent, a lot of people still come from U.S. to do the inspections because we only have very few people there. We cannot do all the inspections that need to be done in India.

JS: So, most are done by…

MT: I don't know the exact numbers, but I'm pretty sure there's still a lot of ORA folks who come [from the U.S. to India] and do the inspections. Especially for the clinical inspection, there are people who come from the BIMO foreign cadre. There is a separate foreign cadre of inspectors now. The FDA inspectors locally are sometimes called upon to assist them [or do inspections on their own]. If there is like a for-cause inspection, they would say, [India Office] go and do it directly because we want [a] shorter time [window] to [initiate] that inspection.

The other point I also want to make is getting an inspector to come to India to do an inspection cannot be done totally without anybody knowing about it, because obviously the person has to get a visa to come to the country. And they are coming on an official passport, so it has to be cleared by the government officials there. So, the government knows that somebody from the U.S. government is coming there and the purpose for the visit is an inspection. They may not know where they're coming to do the inspection, but there is this assumption that we could do unannounced, totally, not a whole lot. We can do that with the folks in India, and that is where the inspectors in India are valuable. You can send them for some [data gathering, which] are not just inspections. But otherwise, the systems are such that even if you're going to go to a hotel [near] where a company is located, the hotel immediately is going to tell the company whose nearby, "Hey, there's a guy from FDA who's staying here."

So, it is exceedingly difficult to do these kinds of [unannounced] things. You can think we are doing it totally unannounced, but you can? I am not saying you cannot, but it is difficult to get it done [unannounced] that way. And when you do find things [inspectional observations or regulatory violations], obviously you are dealing [working] in another country, you are dealing with another system, and employees are very scared of their supervisors in India. They do not speak much, or sometimes there are communication barriers. So, all these things have to be factored in when we are doing an inspection in a foreign country. And I really applaud our FDA inspectors who go there and work in these difficult, difficult conditions.

I know some FDA inspectors who have had to go to a place where there is an airport and drive four hours. [They] get a taxi and drive four hours to where the actual site is and then do the inspections. So, it is not as what you would say, going from here to North Carolina, staying in a hotel, taking your own car, or rental car and driving to the facility.

It is incredibly challenging sometimes. But our folks, I applaud them. They really work hard and they do a tremendous job. I always have tremendous respect for all our FDA inspectors. They have a lot of courage. It takes a lot of courage to go [to an environment that is not really inviting you] and do the work they are doing for us.

JS: It sometimes seems just overwhelming that we have so many - a discrete number of inspectors, whether they're in country or coming from the States, to deal with just so many establishments. And so, and considering how much of our APIs, our Active Pharmaceutical Ingredients are imported many, a large part from India of course, and the other commodities you mentioned. How does one deal with that reality of a discrete number of people who can deliver only so many inspections with an industry so widespread?

MT: I missed [saying], after seeing all this and being involved in all this, all I can say is I am just simply fascinated that this system [FDA's oversight] works. Although we are doing a small part of what really could be done, the system somehow is working, and I really think it is [working] because the basic human nature is that they want to do the right thing.

There are only a few elements here and there that always want to get ahead by doing the wrong thing. And that is the challenge for us, to find, identify those, and weed out those [entities]. But I think most people want to do a decent job and get away with it. And that is reflected in our numbers of findings, usually.

In the GCP area, if you look, most of the inspections we do, about a half of them are NAI (no action indicated) inspections. We do not find anything. It's NAI. There is another 45% of which may be having some problems. And they are classified VAI. There is only about 5%, usually – I think the range is between 3 to 8%, where you do find problematic studies/data.

And that's very reassuring that out there in the world, and that pattern has held consistently over the years. It is not like there's blips and so.

JS: How does that compare to what one might encounter in the States with similar types of inspections? Comparing the NAIs and VI and –

MT: Oh, the numbers I was talking about were generally globally really, I was not separating foreign and domestic. I am glad you brought that point up. I was not separating, I was just talking about things globally, but I think U.S. also is the same. Same, same pattern. Fortunately, there is only few inspections where we run into major problems.

Most people try to do a decent job. Some people make mistakes and then they correct them, and they move on.

JS: So, you had mentioned previously, I asked about staffing, and staffing poses challenges, I know. And it speaks to what I wanted to ask about, which is this designation of so-called hardship locations. I guess the State Department has such a designation. They must define it somehow. But is New Delhi, is that considered hardship?

MT: I mean, relatively speaking, I don't think New Delhi would be considered a hardship posting. Although, one could argue that because of the air quality, and the living conditions and all that you could claim… but it's usually relative, like a war zone, for example, I think if you go to Afghanistan or Pakistan, I think that would be considered more of a hardship location than New Delhi. New Delhi is a reasonably comfortable place to live in. But that being said, any foreign posting sounds very fancy and yes, it comes with a lot of things that you can brag about.

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Yes, you are representing the U.S. Government in a foreign country. As Director, I was reporting to the Embassy, the Ambassador at the Embassy. And you are exposed to a lot more than just anything limited to FDA. So, all that is the fancy part of the work. But it also means that you are separating from your society where you are living, you are going away for periods of time when you have no more contact with your friends and relatives.

I went there alone. I did not take my wife, so I just was shuttling every few months here, and then going back. But there are people who take their family with them, and yes, that is helpful because now you are exposing them to living in a different country and meet different people and all that.

But again, they are all subject to some level of stress also, because they are now breaking away from their society. They are going there and they have to live with all the different people, and culture and everything. So, there is good and bad and it is a balance of everything. And ultimately, I think there's a lot that’s good that comes out of it.

So, I again, applaud the people who make the decision to go and work in these posts. It is not as easy and rosy as what you would think it is. It comes with its own challenges.

JS: I'm sure it does. You had mentioned India was in the process of developing a new regulatory system, a national regulatory system, I believe. And I recall seeing references to the office, at least at that time, lending some assistance, counsel, what have you, as this new regulatory system was blossoming. And I'm wondering if that was still the experience, this was still sort of a relationship, if you will, between the India office and the national system.Was there any counsel that the FDA could provide, or was asked to provide, in terms of e this new regulatory system in India?

MT: Yeah, I think Indian regulations pretty much are from the 1945 pre-independence regulations that the British had. And it is constantly evolving.

There's new changes happening, there are new things that India has been doing, and there is a lot of consulting we do between the India Office and the Government of India regulators. And one of that is the process through which we do the training. We tell them how we do our inspections, we train them how they could do the inspections.

One of the things I worked with them is to develop a Handbook For Clinical Investigators, because the clinical investigators in India, or the people who were assessing clinical investigators, did not do things the same way we did. It is a different culture. It is trying to tell people in India what the importance of getting informed consent [is], there is a different way they look at it.

So, informed consent, doing clinical trials the right way, all this are evolving concepts... there's a lot of mutual exchange of information that we have been doing. And I think it has been extremely helpful for both of us. We are able to understand what they do and what their limitations are, and they're understanding what we do and what our limitations are, and so it's a process of growing together. I think it has been immensely helpful.

JS: The last thing I want to ask you about jumps forward a little bit to the time when you're in the Office of Generic Drugs and the global affairs part of that. One of the responsibilities you had in that position was in training, international drugs, generic drugs, regulators and stakeholders, and industry stakeholders rather. And I'm just wondering if there was anything you pulled from your India experience in that part of the responsibilities you had in OGD at the time. What, if anything, had you learned from your India experience that could be applied in your subsequent position in OGD?

MT: I do not think I trained anybody. I was trying to explain how the Indian drug regulatory system and the generic drug industry in India was working, and I had some ideas of how to strategically start working with them more closely so that we could get a lot more confidence in what we are getting from India.

Mine was only a detail in OGD for a period of, I believe, four months. I think initially it was three months. I think I may have extended it; I do not know if it was four months or six months, total. I know there was an extension somewhere. And then I came back to OSI, and I had

laid down a strategic plan for how we could improve this information flow between the generic drug industry in India and the OGD.

Obviously, I was not there long enough to execute it and get it up there, but I had some ideas of how we could do it. So that may be what you are alluding to. I laid out, I still have that kind of a strategic vision on how – because the few things I have learned over the years is we cannot do everything by ourselves.

The playing field is so huge, and we are, in spite of how big the FDA is, there's only limited amount of information we can go and get. And all this involves money and time and personnel and everything. So, the more collaborative we become, and when I say collaborative, we have to first establish a level of trust. And if we are able to establish that level of trust and then collaborate, then I think we can minimize our efforts and maximize the amount of information we are collecting. It will be useful.

JS: Great. Just a couple more. One thing I noticed after you had returned to OSI following the position in India.I'm not sure to what extent, but you were involved in issues of Artificial Intelligence policies in CDER and I'm just curious, I don't know what you can discuss, but what kind of points came up? What kind of issues came up that CDER might have been concerned with, in terms of AI? I can't say I've heard too much about this.

MT: Again, I think it is this hand that directed me into the Artificial Intelligence space. I don't think I was in any way qualified to be in that team, but it was by default that I just got involved

in the AI steering committee. But it turned out to be a phenomenal learning experience of where things are today and where things are going to go into the future.

As we all know, Artificial Intelligence is now dominating the news, pretty much in every sphere of life, and to a great extent, whether we realize it or not, we are using Artificial Intelligence pretty much every day, to varying degrees. Every time you try to type something on your phone, it is correcting you and it is telling you, is this the next word you want? So, it is already doing that.

And then translations, you can just get the computer to translate stuff, so there is a lot of stuff that we use. How this is going to play out into our regulatory space, is the big question. And for me, more specifically, this is where I like the opportunity of being in the AI steering committee, is how do we trust the data that is coming in, that is now being generated through Artificial Intelligence?

I have attended talks where people could literally, by a process called twinning, generate data from multiple people who don't really exist. You can just take data from a large sample of people, and then you can create a normal database with 300 people. You can just tell it [the AI tool] to do it, and it [the AI tool] can do it [the work] for you.

So, in the real-world setting, now, if somebody gives you information, what are the things that really need to factored-in on whether, number one, can you accept that data? And number two, if you cannot accept that data, how do you go about teasing that data to figure out what is true and what may not be true? Those are challenges that people are learning.

And in the AI steering committee, one of my discussions has been, I think the industry is doing a lot more than what we know. So, I thought rather than reinventing the wheel from the

beginning, we should use more discussions with the industry that is using it [AI tools] to learn what they're doing, to find out what they consider the problems, and then figuring out how to apply that in our own setting.

JS: It's not quite like the old days of a rogue clinical investigator dreaming up data to send with the results to a sponsor.

MT: This may not be a person involved. It could be a computer [algorithm]. What are you going to do with it? Yeah, so I mean, not everything with AI is bad. I think AI offers so much potential in various facets of life. But, I think, over time we will figure out a way. I think humanity has always figured out a way to deal with issues, and I think we will. But it's a very interesting place in time right now, where you see a tremendous value of AI, but you're also seeing a tremendous potential for AI to do harm.

So how do we sort this out? The good and the bad? This is going to be the challenge of, I think, the next several years.

JS: So, this is very much on the agency's radar?

MT: Yes. And I think we have a lot of interested, dedicated people who are struggling with these issues as we speak.

JS: We've covered a lot of territory here, but I wanted to give you a chance, if there's something that absolutely must come out that I haven't asked you about yet. I always like to do that at the end. Just to make sure we covered –

MT: I think you have covered a lot more detail than I expected you to cover. You seem to be knowing more about me than what I know [remember] about myself!

JS: There is a lot to talk about here. I probably should ask, you have, in your career here, you've mentioned following the hand. But you have pursued just a wide variety of interesting fellowships and various appointments, even details.

And, either you have one heck of a thirst for adventure or you love multitasking or you just like a large variety of intellectual challenges, but, it's an element to your career that I wonder, reflecting back, you seem to like being in lots of different positions and learning from those.

MT: I always, right from my school days, I am somebody who sees a situation and I like taking it on and I like getting engaged in it. And when I get engaged in something, I put my heart and soul into it. I just do not do it for a paycheck. And that attitude of mine, I think, has played out in my life. Every situation I've been in, whether it's here at the FDA or outside of FDA, when I get involved in something, I bring a certain level of passion to it.

And I have been blessed with phenomenal opportunities, opportunities that do not come by to everybody. And I have been also blessed with a fantastic array of people that I have crossed

paths with and worked with. Some of them, as you mentioned, are legends that history will always remember. But even otherwise, even the people I have worked with, and I do not like saying people who worked [for me]. I would rather say people who were on my staff [my colleagues], in various situations, [they were] fantastic people.

And, here and there, I might have had one or two people who I could have been without having to deal with, but that's life, right? But most of the people that I have worked with have been so wonderful. They have been so helpful, and we have always worked as a team. And I come from a culture where especially, if I was a supervisor, I always felt that I had every person working in my team confident that I have their back. And that confidence has let them do their thing with the confidence that my boss has my back. And I have enjoyed it. I think most of them enjoyed it. And I will take many fond memories from this journey in FDA. When I started [at FDA], I said, it is not something I really knew about or what I was landing in when I took it on. But now at the end of it, I feel that I was kind of meant to do this [journey through FDA]. It is almost like this was my calling and I'll leave it [FDA] with very fond memories.

And, thanks to the agency as a whole, my thanks to all the people I have worked with, they have all educated me. All those FDA inspectors that I've worked with, I've done about - almost 90 [or more] inspections. Each of those FDA inspectors have taught me something in my life. So, all my supervisors, they have all taught me something. So, it has really been an amazing journey]. I do not even know how to express it more than what I have already said.

And particularly I think my - I would be remiss if I do not say this. I guess because of my association with Dr. Kelsey, I got to know you as a person. And I don't know how many people in the FDA get a chance to work with people in the History Office, but I think you have taught me a lot about the history of FDA. I learned a lot about your office through you and I remember

visiting Kelsey with you. So, there is so many memories that you personally have also enriched my life with.

JS: I appreciate that. We had a splendid time planning the first Frances Kelsey Award for Excellence and Courage in Protecting the Public Health, didn't we, when Dr. Kelsey and her family came to White Oak to get the very first award from Dr. Hamburg. Anyway, it's been a pleasure. Mathew, thank you for doing this and doing a little bit longer than I had said it would take. But I appreciate it very much. And with that, I think we'll –

MT: One last word. My apologies if I misspoke anything, when we look at the transcript, we will see. My apologies in advance for somebody who says, “No, that's not what he [should have] said, that's not accurate.” I will stand corrected if you correct me [with evidence].

JS: Very, very well. Thank you again.

MT: No problem. Thank you.