History

of the

U.S. Food and Drug Administration

Interviewee: **Andrew C. von Eschenbach, M.D.**

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

Date: **September 15, 2013**

Place: **Philadelphia, PA**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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GENERAL TOPIC OF INTERVIEW: History of the Food and Drug Administration

DATE: September 25, 2013 PLACE: Marriott Hotel, Philadelphia Airport Philadelphia, PA LENGTH:

INTERVIEWEE:

NAME: Andrew von Eschenbach, M.D.

ADDRESS:

INTERVIEWER(S):

NAME: John P. Swann, Ph.D.

ADDRESS: History Office, Food and Drug Administration

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Andrew von Eschenbach

September 25, 2013

TAPE 1, SIDE A

JS: First of all, thank you, Dr. von Eschenbach, for joining us for an oral history. We're meeting here on September 25, 2013, in Philadelphia, at the Marriott Hotel at the Philadelphia airport. As you can tell, there's a lot of traffic here, but I think we'll be able to hear most of the conversation.

What I want to start with is just some background, your family background and the influences on your career, if there were any specific interests in medicine and urology, urologic surgery,that shaped your background. But maybe what we should do is start about where you were born and educated at first.

AvE: Well, you're close by, basically a kid from South Philly. I was born not very far from here as we're sitting here in the airport. I grew up in Philadelphia. My education was here except for medical school, when I went to Georgetown Medical School. And I went to a Jesuit high school and a Jesuit university here, so I have to say that 12 years of Jesuit education had an impact. It

pointed me in a direction of wanting my life to make a difference and to, in some way or other, contribute to other people. I started out thinking that that would be a career in the military, and I was hoping to go to West Point from here, but that didn't happen. And my next focus was then on a career in science, and I started out as an electronic physicist, didn't quite complete that, found out I wasn't as excited about that kind of a career because it didn't have the personal interactions.

So basically I'm a people person. I love working with people and being involved with people, and so I switched out of physics into biology, to pre-med.

There's an interesting sidebar story to that, about my early career in college. Suffice it to say I was spending probably more time still hanging out on the corner in South Philly playing cards than I was studying, and it took a little bit of an awakening and a bit of enlightenment on the part of my father and the Jesuit priest to kind of get me back on track. Fortunately, that track went very well. As I came to the end of my medical school career, I worked all through medical school. My parents were not financially well-off, and I was the first in my whole family to ever go to college.

JS: What did your parents do?

AvE: My father was a tool and die maker, and my mother, in order to help with my education and my brothers' education, worked as a clerk in the courts. Ultimately, my father did that as well here in Philadelphia.

But I worked through medical school, and in order to kind of finish it, I had to join the Navy in the senior medical program, so I was commissioned as an ensign with orders to go to medical school, and when I finished that, I came back to Philadelphia, did an internship in general surgery at Philadelphia General and the University of Penn, and then went into the Navy for three years.

JS: Where were you?

AvE: Stationed in Washington, D.C. As a matter of fact, at the Washington Navy Yard, where we just had all this tragedy occur.[1]

And the point of that was I left going into the Navy fully expecting I was going to pursue a career in general surgery, but in coming back, I actually came back to a residency in urology. So I started then to be a urologist. But as I was doing my residency in urology, I really became fascinated with oncology, and that led me to wanting to do a fellowship, which I would have done up at Sloan-Kettering

[1] Editor's note: On the morning of September 16, 2013, a lone gunman fatally shot 12 people and injured three others in a shooting at the headquarters of the Naval Sea Systems Command (NAVSEA) inside the Washington Navy Yard in Southeast Washington, D.C.

in New York, and circumstances were a bit unusual. A mentor of mine had gone down to Texas to become chairman of the Department of Urology at the medical school in Houston, and he suggested I come down and look at this M.D. Anderson Cancer Center before making up my mind. By that time, Madelyn, who was my first date in the sixth grade and with whom I grew up in South Philly, we were married and had four little kids, and she wasn't terribly anxious about living in Manhattan in a small little apartment with four little kids. So we said, "Hey, we'll go to Texas for a year. That could be kind of fun. The kids might enjoy seeing cowboys and things of that sort."

So we went to do a fellowship at M.D. Anderson fully expecting I'd come back after a year to home and to the University of Penn, where I was on the faculty, but we stayed at M.D. Anderson for the rest of my career, 26 years. The kids grew up there; they're Texans.

But then my career there went through a series of changes, and I emphasize that because when I went to M.D. Anderson, I went as a Fellow. It was in 1976, and I had the privilege over those 26 years to really be a part of a major transformation in medicine. I started out in my career at a time when we were saddled with the historical perspective of medicine in which what we were doing was

based on our observation of the manifestations of disease. We could feel a lump in a woman's breast and say it was breast cancer, or we could see a shadow on an x-ray and call it pneumonia. But observing manifestations of disease didn't really help us figure out what to do about them. That was all empiric. It was all a matter of a trial of this or a trial of that.

But as I was going through my career, cancer was leading a biomedical revolution. We were now probing these diseases at their genetic, molecular, and cellular level, and what we were doing was moving away from just observing manifestations to now understanding fundamental mechanisms. We began to understand the problem in a profound kind of way. And that understanding was leading us to more rational, intuitive interventions. So that transformation was really positioning us, using cancer as a model system, to transform the entire future of medicine and ultimately of healthcare, because we would be moving from empiric medicine to rational medicine, from interventions that were disconnected from the disease to interventions that were logical extensions of our understanding of the disease.

And so when I had the opportunity to go from M.D. Anderson to become the Director of the National Cancer Institute, that was an opportunity for me to really help

contribute to the orchestration of this new agenda. From 1970 on, we were really blessed, by virtue of the passage of the National Cancer Act, 1971, which was a profound piece of legislation that basically was built on the Yarborough Report, which was a report that was commissioned by Congress. Senator Yarborough was the head of that commission. And the Commission, for the first time, really began to look at the opportunities that research, cancer research, could create, and the Yarborough report heralded the molecular-medicine era.

The subsequent passage of the Cancer Act empowered the NCI to really capitalize on this emerging opportunity in science and technology and some of the subtle things that were maybe not as apparent at the time, even allowing the FDA, I'm sorry, the NCI to employ contracts as well as grant mechanisms. So, without going into that story in a long way because this is not a history of the NCI, it's a history of the FDA, but the point is the NCI was leading this transformation, and it was building an infrastructure like our cancer center infrastructure so that by the time the 20th century came to a close, we had 63 NCI-designated cancer centers in this country, the likes of which, like Sloan-Kettering, M.D. Anderson, Dana Farber, Fred

Hutchinson, on and on and on, nothing exists like that in the universe.

There were only three cancer centers prior to the Act. There was Roswell Park, Sloan-Kettering, and M.D. Anderson. But by virtue of these new authorities that the NCI had, by virtue of the investment that was being made and the funding, the NCI was able to create not only the cancer center network, but the clinical trials network, the cooperative groups emerge, like ECOG and SWOG and others.

So what I was privileged to do in 2002, when I arrived in Washington to be the Director of the National Cancer Institute, was to inherit this incredible infrastructure that we as a nation have created. And the goal was, at that time, to capitalize on that infrastructure, to mobilize the resources and integrate and coordinate them in a strategic kind of way that would enable us to use the fruits of that research enterprise and research effort and strategically attack the problem of cancer in a way that, since we now are understanding cancer, not as an event that occurred in someone's life, but a process, and that process had a beginning with your susceptibility, whether it was your genetic makeup or BCRA gene or an exposure to something in your environment, and then a process of transformation, a process of growth, invasion, metastasis,

and ultimately death. And we could now begin to see that process, map that process, understand fundamental mechanisms along the way of that process, and now begin to tactically create interventions to intervene in that process.

JS: And were those interventions primarily pharmaceutical?

AvE: The interventions were obviously initially pharmaceutical, but what was occurring, because of our understanding of mechanisms, is that we were seeing more opportunities for biological interventions, and we were moving from small molecules to now being able to see the fruits of monoclonal antibodies, for example, and the benefits of recombinant DNA technologies.

The point, however, was that now that we could see this amazing opportunity to capitalize and use cancer as a paradigm for a new future in medicine, the pieces of discovery were there and the pieces of development were there, but nothing could be delivered until everything, at some point in time, went through the FDA.

So, as one was sitting there at the NIH and at the NCI looking at this amazing terrain of opportunity, it was apparent that all of that would sit fallow unless and until it was aligned with the regulatory pathway that would

enable it to be delivered to patients, to people who were in need. And at the end of the day, savings lives and improving health was the only thing that mattered; that was the only thing that counted. The only thing that's important in our commitment to research and development is that we're going to help another human being. We couldn't do that without the FDA.

So I recognized, even as the NCI Director, that the FDA was critically important to anything and everything we hoped to accomplish. And when Mark McClellan was confirmed as Commissioner on a Thursday night at about nine o'clock, that next morning, that Friday morning, I was in his office at the Executive Office Building, because at that time he was still in the White House staff as an economic advisor to President Bush's domestic policy. And he and I met that following morning after his confirmation with the conversation around the fact that anything and everything I hoped to accomplish at NCI in eliminating suffering and death due to cancer could not, would not happen without the FDA as a partner. And he, in terms of his mission for FDA of wanting it to be a bridge and not a barrier to new solutions for people, could see the NCI as an extremely important strategic partner who had this enterprise that was turning out, at almost exponential growth, new

opportunities, new drugs, new interventions, new clinical trials that would be able to provide data and information.

So we put together the joint NCI-FDA Task Force, and the idea was to bring our two communities together and begin to create a dialogue, a mutual understanding of common goals and common opportunities to work and collaborate, to align discovery and development with the regulatory pathway that would ultimately lead to new, mindboggling interventions and opportunities to save lives.

JS: Had you engaged his predecessors after you came to NCI?

AvE: Well, Jane Henney was actually my next-door neighbor as I lived on the NIH campus. But by the time I arrived in January of 2002, Jane was no longer the FDA Commissioner. And, as you know, there was a period of temporary commissioners. I did establish a very early relationship with Les Crawford, and we had mutual friends that introduced us. So I had a relationship with Les, but it wasn't until we had a confirmed, Senate-confirmed Commissioner, that we could really begin to implement the kind of relationship-building and the kind of, if you will, agreements that would be necessary.

JS: And that’s something you would certainly appreciate, having been in both positions as both an Acting Commissioner and as a confirmed Commissioner.

AvE: Right.

So that began. And the reason I emphasize that is because although my arrival as the FDA Commissioner was somewhat precipitous, it was not with a total lack of appreciation or understanding of the critical important role that FDA plays.

JS: Along the lines of what you’ve been talking about, you were quoted in an *AP* story -- and I hope quoted accurately; I’m going to reference just a couple sentences here -- but I think it points out a lot of the themes that you’re talking about. This was shortly after you became the Acting Commissioner, when President Bush appointed you the Acting Commissioner shortly after Dr. Crawford resigned. And you said, I believe very strongly, science has to drive and is the driver of our knowledge and our understanding and, therefore, of our decisions. Where science is incomplete, we continue to believe that, under any circumstances, do no harm, but in the same piece you were also quoted, I believe, it’s still important to ask the question, how can we accelerate the timeline? How can we

make certain we're getting these interventions to the patients as quickly as possible?

And so I guess you had a perspective here from both sides of the equation where you're developing therapies as quickly as you can because you're treating the patients. But then, from the FDA standpoint, there's also the issue of, well, the therapies have to be provided, but they have to be provided in a certain context that protects the patients. Now, protection can mean protection from harm, from what the medicine itself might deliver, but it's also an issue of, are you preventing access to the therapy? So I guess what always puzzles me is, how does one bring all these mechanisms together in place? Now, maybe that alignment between NCI and FDA when Dr. McClellan was the Commissioner, maybe that's part of the process. But it's always a challenge, isn't it?

AvE: Well, I think in many ways the reason I emphasized my background and my early development is because I think we're a product of our backgrounds and our early development. I start out first and foremost as someone who's inquisitive. I wanted to always know how things worked. That's what led me to an interest in science and in physics, and then ultimately in biology. I want to understand. I want to probe those mysteries. And

when I encountered cancer, oncology, that was the mother of all mysteries in the sense of, how does this happen? What is going on here? So cancer was initially for me an intellectual exercise. It was an intellectual pursuit. It was about satisfying my curiosity. And I found myself in a place like M.D. Anderson where I could satisfy anything I wanted. I had any question, there was somebody I could find in that institution that was interested in researching or studying that question. So it was like being in heaven as far as anyone who was inquisitive and wanted to probe and understand and do research. But at the same time, every single day I was in that institution, someone was suffering and dying right in front of me from that disease. So cancer for me was not just an intellectual exercise. It was a matter of life and death and horrendous suffering. To watch someone with metastatic prostate cancer, like my father, writhe in pain and die a dehumanizing kind of death is not acceptable.

So when I came to NCI, I came with the attitude that yes, research is absolutely critical. Without it, we go nowhere. Without it, we know nothing. But this isn't about doing research. Research is not the end. It's the means to an end. The end is that we need to save lives and eliminate suffering. That's why I set the goal. It's

because now we had this research leading us to a whole new way of seeing and understanding this disease that made it possible for us to reach that end, to strive for that end.

And when I came to FDA, it wasn't simply that we're there to process data, whether it's a drug application or adverse event. It's that we were to be a pathway, a bridge, to bringing all the promise and all the fruits of our research and development to patients and make a difference in their lives. Now, we have to do that with rigor and precision and discipline. We have to do that in a way that we do no harm. It's not enough to say that a patient has a problem and I have the answer. It's an operation. You have to also do that operation in the appropriate, correct way and do no harm.

So my mantra was, let's see our goal as saving lives and improving health and well-being, and let's do that with a sense of urgency, let's do that with a sense of passion and commitment. But at the same time, let's do that with the rigor and precision and discipline that makes sure that we're doing it properly and correctly.

JS: It's interesting to hear you talk about setting goals, because you did set a goal, a very ambitious goal, when you were at NCI. It was a goal.

AvE: It was a goal.

JS: It was a goal of ending suffering and death.

AvE: Eliminate suffering and death. We're not going to cure cancer, but eliminate suffering and death.

JS: Making it a manageable disease.

AvE: Exactly.

JS: I think what you said, by 2015.

AvE: 2015.

JS: Where did that come from? I just am curious. Where did that come from, and why did you say it at the time you did?

AvE: Well, it came from probably what was a naïve belief when I came to Washington. I actually came to Washington believing that if you set bold and audacious goals, like put a man on the moon and bring him back in a decade, and I could show you how we could do that, that everybody would say, well, why wouldn't we do that; let's do that. And so I set a goal, and the goal was to see cancer as a process, to recognize the fact that we could identify a variety of steps along the way in that process; and if we started to mobilize and collaborate, cooperate, and use the incredible resources that were already in place, we could start to strategically intervene in that process and either prevent it from happening in the first

place; we could detect it much earlier and thereby eliminate it; or we could modulate or change its behavior.

So, for example, I know this. If suffering and death, if the endpoint of that process is what my target is going to be, I now have a whole host of ways that I could affect that outcome. With the exception of brain cancer, people don't die of cancer; they die of metastasis from cancer. If I can detect any cancer early enough, we can eliminate it already. So we didn't have to discover anything. We just had to be able to find it earlier.

If I was to alter one single step in the cancer process, namely the metastasis, the transformation to a metastatic phenotype, I could radically, dramatically change the death rates. If I could detect lung cancer earlier, I could radically, dramatically change death rates, because that was the biggie. So why did we put so much effort into and so much support and funding behind the National Lung Cancer Screening Trial? It's because there was a disease that, if we just improved how we could detect it, we could make a difference. Other diseases, maybe it was somewhere else in that spectrum.

But the point was, is to set a goal to describe a rational way of achieving that goal, to then get the collaboration and the buy-in to coordinate and integrate,

and to synergize and to nurture or support where we needed to, to create a massive Manhattan Project or NASA, in a virtual kind of way, if you will.

The problem was that I was too naïve, and I believe that the expression of a goal would be welcomed. Instead, it met with a huge amount of resistance, and the first thing that happened was a very difficult editorial in *Science* magazine.

JS: But was it met with resistance within the Center?

AvE: I think it was broadly. It was maybe too bold and too audacious, and I did not do a good enough job of putting in place or laying the groundwork for it, so I take responsibility for that.

JS: Well, I guess what one tries to do as a leader of institutions is inspire, among other things; not that that was necessarily the sole or the primary thing behind what you said, but others who've set radical goals have inspired people.

AvE: And if I look back on it, I began a conversation and I began to help create an awareness that maybe there was a new opportunity before us now that didn't exist before. Maybe we no longer were blindly throwing darts at a dartboard, hoping one of them would hit the bull's eye;

that we, instead of being empiric, we could be strategic, we could be rational; that we should, as we understood more about fundamental mechanisms, we should be immediately thinking about what does that mechanism imply in terms of what I should do about it. And we saw the Gleevec story in chronic myelogenous leukemia unfold.

I mean, I already knew that the death rates for cancer were going down. I already knew that we were seeing the fruits of this new approach to cancer being more rational. The data that we were working from in 2002, you know, basically SEER data are old data. If you're on the frontlines, as I was, at M.D. Anderson, you could see it happening on the frontlines. Even though it took a long time for that to become apparent in surveillance reports at a macro level, we knew it was occurring at the micro level. And in many ways, that kind of epitomizes my evolution, if you will.

I talked a little bit about what I was, what shaped me upon my arrival. But the truth of the matter is, as I look back on it now, my time at M.D. Anderson was just that, boots on the ground. I was engaged in hand-to-hand combat, and I was on the frontlines, and I was smelling the gunpowder, I was seeing the death, and I was engaged in the research. I was Chief Academic Officer and Executive Vice

President at M.D. Anderson, so I was responsible for a thousand faculty and all the things that were going on at the number-one cancer center.

And then I got to NCI, I got to NIH, and that was like going from boots-on-the-ground to an AWACS plane, because I really got to fly over the terrain, I really got to see the whole battlefield and visit our cancer centers and realize the power that existed within that infrastructure if we could more effectively utilize it, if we could break down some of the silos, if we could drive greater collaboration and coordination and integration among the cancer centers.

So when I was NCI Director, I called a retreat of all the cancer center Directors to come to Washington, all of them, every single one of them, at one time to meet with me and spend two days talking about the strategic agenda for our national cancer centers program. It was the first time that it ever happened. And some, one in particular, refused to come. So there were barriers and there were obstacles to the kind of integration, coordination, I believe were needed. I think Homeland Security is still faced that with the integration of some of our intelligence agencies.

JS: How did FDA fit into this equation at this point in time?

AvE: Well, in terms of the task force, Mark and I did a number of things, one of which was we wanted to start a joint training program, because at the end of the day, to change culture, you change people, and the wonderful way to change people is to bring bright, new, fresh faces and minds into the environment to basically start breaking some of the barriers.

JS: So, were the people who were involved in review of oncologic drug products, were they pulled into this as well?

AvE: You know, that initiative didn't really get off the ground as extensively, as much as we'd have liked it to. What ultimately wound up happening, after four years at NCI, in my fourth year then, of course, the phone rang on a Thursday night, and it was the White House, and the essence of the conversation, in short, was that the next morning, Commissioner Crawford was going to announce his resignation, and would I come over, take over at FDA, and that's a whole interesting conversational story unto itself.

But, as you know, the bottom line of that was, the next morning, his resignation was announced and my appointment as Acting Director was announced. Over the weekend I had intensive meetings, a phone conversation with

Mark, and by Monday morning Secretary Leavitt and I showed up at the FDA Headquarters at Parklawn and I met all of you as your Acting Commissioner, and for six months I did both jobs. So I would start at NCI in the morning, very early, as a surgeon usually does, and then I'd come over to FDA mid-morning and stay till late afternoon and leave, and then go back to NCI and stay till whatever time it took at night, and did that for six months, because at the outset it was not, it was an intervention on my part. It was not intended to be a permanent transformation.

But when I got to FDA, as much as I had an appreciation and awareness of the institution, what I didn't have was an understanding and appreciation of the stress and the incredible duress that the institution was under.

JS: The rumor at the time was that you arrived, saw what our budget was, and thought there must be some sort of error here; the decimal was in the wrong place or something.

AvE: Yeah. It was pretty close to the truth. You know, I was sitting at one desk where I had almost $5 billion to give away or to deal with, and I had more friends than I knew; I had some relatives I didn't know I had. And then I came over to my other institution, where I

think at that point, as far as federal funding was concerned, that worked out to about $1.2 billion, if I remember the numbers correctly, regulating 25 percent, almost, of everything Americans consumed, from tongue depressors and lettuce all the way to wondrous monoclonal antibodies and everything else.

You know, when I arrived, like most, I guess, executives would or should, I had to do an assessment. I asked myself some fundamental questions like, okay, so what is this business that you are the new CEO of or the Acting CEO of? What does it actually do? And in its most simplistic terms, the FDA is really a data management business. It doesn't make anything; it doesn't produce drugs; it doesn't make widgets.

What FDA does in its most simplistic form, if you will, is it acquires data, and it then has to aggregate that data, analyze it, put it into a context called policy or regs or whatever, and then it acts, makes a decision. So the data can come in in a variety of different flavors. It can come in in the form of an IND or an NDA; it can come in the form of adverse-event reports or whatever, but it's simply, the data comes in and a process occurs and there's an output, which is a decision.

So I said okay. Now, what are the two most critical things, critical assets, that you have to have for that kind of a business? One is intellectual capital, and the other is you have to have tools, information management tools. So I said okay, let me look at my intellectual capital, and I quickly got people going off getting me data, because I'm a data guy. And, oh my God, you're kidding me. The workforce has been shrinking as the demands and everything else are going up? And it's shrinking not in terms of any rational kind of reapportionment. It's just shrinking by virtue of attrition in various little cubbyholes and whatever. But yet our demands are not expanding uniformly. They're occurring in various pockets, like imports are going off the charts and all this kind of stuff. So now I've got a mismatch, but I've got a workforce that's going down and a big demand, a workload, that's going up. So let's look at the workforce even though it's diminishing. No one under the age of 30; average age was 47. Thirty percent of the workforce had either reached retirement or was eligible for retirement. So one third of this workforce could walk out the door tomorrow and probably be better off in terms of getting another job with more money, and this, that, and the other thing. And it's like, oh no, this can't be true.

Information technologies and infrastructure. There's a thing called a Gantt chart that I wish I could still have a copy of. The servers and everything else across the agency were pre-Y2K for the most part. We were spending $200 million a year maintaining junk. We could not get vendors that could even keep up with because there no longer were replacement parts. None of the servers across the institution communicated with each other. They were working, if I remember the numbers right, something like 30 percent efficiency, whereas it should be somewhere up around 80; on and on and on and on.

So what's my point of all this? I quickly was going through, like any doctor would who was called in to see a patient as a consultant, I was going through the diagnostics. And what you do at the beginning of your diagnostics is you go look at the chart. Right? So you read all the data in the chart. And I'm reading the data on this patient, and it's like, you've got to be kidding me. And then I go look at the x-rays and the EKG and everything else. And then I come to the conclusion, before I actually go in and see the patient, that, why did you call me? This patient is dead. No one could survive with these kinds of numbers, so what am I doing here? Well, you walk in the patient's room and there's this vibrant,

active, incredibly positive human being lying in the bed, and you say, “I must have the wrong patient.”

The point of that story is, when I looked at the numbers, I thought, this agency has got to be out of business. And yet when I met the people and saw the people, it was the most incredible agency I ever could have imagined. Not only were they succeeding, but they were doing heroic things. They were carrying the load on their shoulders that long ago would have crushed anybody else, long ago would have put any of them in business, out of business. There should have been catastrophic failure. But they weren’t; they were coping. But that didn’t mean that catastrophic failure was not on the horizon. We had to make some changes. We had to do some things, because at this, they could only carry it so long.

I remember one of my first meetings with the Center Directors was a meeting in which Bob Brackett, God bless him, who was head of CFSAN, said to me, because I’m talking about, wait a minute, we’ve got to fix this and we’ve got to shore this up. We’ve got something, an attack coming over here. I need to move over here and defend that wall. And he says, “Commissioner, we are so far beyond doing more with less. We can’t do any more; we can’t do that. The only thing we can do from here on in is less. We’ve long

ago been tapped out." And I realized he was right, that from this point on, this institution was going to go down. It just couldn't go any other way. They were way, way beyond climbing that hill.

So, what that did was, with all the hopes and expectations that we might have had with regard to the role that FDA could play, the first job I had was to resuscitate the agency before I could rehabilitate the agency, before talking about all the things we could be doing about bringing these new and wonderful opportunities to patients, of streamlining the regulatory pathway; of embracing integrated, interoperable solutions that were clearly going to be the byproducts of regenerative medicine and stem-cell biology; beginning to put together diagnostics and therapeutics, things that were obvious in oncology that were the next step, what this molecular metamorphosis was actually leading to. All these things were sitting there in the research-and-development pipeline, because I had just, I was living in that world; I knew what was coming. We weren't ready for that; we could not get ready for that. So, resuscitation became the issue, which meant getting more money and getting more personnel and beginning to create a workforce.

JS: Now, the state of the agency at the time -- was this an across-the-board problem? Did some Centers have more problems than others in terms of this kind of infrastructure?

AvE: Yes. As I said at the beginning of this conversation, this really is a book, it's not a conversation. The complexity was just enormous. I mean, first of all, when you got into the structure, you realized that there were anomalies within the structure, both macro and micro. For example, one of the micro anomalies was the distribution of user fees. Some centers had user fees; others didn't. And the anomaly that that was introducing into the system was, in order to protect the user fees, you had to meet the goals that were committed to for those user fees, so appropriated dollars were obviously needing to be secured so that the infrastructure was adequate to meet those goals so that then we could procure the user fees. But that left other centers that did not have user fees without any supplemental sources of support. And the way Congress basically earmarks or -- that's probably the wrong word to use in an interview -- but the way Congress appropriates our budget, it appropriates it according to centers. So you don't have a lot of flexibility to move things around, to take marginal funds from one center and

transfer them over to another center. And even within centers, you don't have a lot of flexibility of moving human capital from one area to another area. So if you can look at your workflow and realize that the demand for . . .

TAPE 1, SIDE B

AvE: So if you see a demand going up in one particular area -- like, for example, it was clear that as we looked at innovation pipelines, that the oncology pipelines were rich with a whole host of innovative, first-in-class kind of drugs coming along -- you don't have the flexibility to move human capital around very easily within the institution, to move, say, someone from, just pick another area, infectious disease, and move them over to oncology and things of that sort. So there are restrictions within the system.

But then there's restrictions outside of the system, because after I was there for a few weeks, six or so, I guess, doing a lot of critical assessments, I went back to the Department and indicated that we really needed an infusion of resources, funds, to meet urgent, critical problems, particularly in IT, information technology. We knew with regard to where we were with the field, that our

IT capabilities at our ports of entry and things of that sort. The problem with the Department's ability and the Secretary's ability to be of support or assistance for that seemed to be prohibitive or stem from the fact that the other macro anomaly is one of budget.

When the President prepares his budget, OMB gives to each of the agencies, cabinets, their mark, and so the Department of Health and Human Services gets a mark, which is that you should prepare a budget according to these following guidelines. Either let's just make, for example, prepare your budget to equal last year's budget; prepare a budget with a 2 percent increase; prepare a budget with a 2 percent decrease. So the Secretaries then go to their various agencies and that flows downhill, which is to say, in preparing your budget for the next fiscal year, I want you to prepare a flat budget, I want you to prepare a 2 percent increased budget, I want you to prepare a 2 percent decreased budget.

JS: Predicated on prior budgets, I guess.

AvE: Right.

JS: Which, as you've been saying, prior budgets can't keep this patient alive.

AvE: Right, right.

So the Secretary has discretion in that he's got a pot that could be 2 percent higher or 2 percent lower or flat for the entire department. He drops that down one layer to the various agencies, who then go about their process like what's going to happen within the various subsets of CMS or CDC or whatever.

So the process plays out where I, as an agency head, am competing with NIH's Director; with CMS's Director, with CDC's Director, with Indian Health, with everybody in HHS. We go to budget meetings and I say, "Yes, I understand that NIH wants an increase and that CDC wants an increase, but I need a 10 percent increase. I can't live with 2 percent, and I can't live with flat or minus 2. We're dying. I need 10 percent more," which means they have to get less in order for him to still be 2+ flat or 2-, because he can't go up 10 percent. Okay? So now I'm fighting with all of them, I'm competing with all of them, I'm making my case, I'm lobbying. I'm driving home all of the arguments. After I get that done and then he says, "Okay, we're going to give you that," I now have to go to OMB and I have to defend it at OMB. Okay. So now the President buys off on it, and everybody's bought off on it and says, "Good, we're going to see that FDA gets a 10 percent increase, and everybody else is going to get minus 2 percent."

At that point it goes to Congress, because the President doesn't give me the money, Congress does. Congress is very jealous of that. They appropriate; the President just recommends. Now, all of the rest of HHS goes over to Health, Education, Labor, and Pensions, and FDA goes over to Agriculture appropriations. Now, at this congressional level, I'm not competing anymore with NIH funds, I'm competing with farm subsidies, etc. So now a whole different conversation has to occur with enlightenment and everything else. So at a micro level, the whole budget process for the FDA is of a nature that does not lend itself to rational, strategic, long-term commitments to create infrastructure that's commensurate with demand and opportunity. It's that simple.

Now, would it be simple and easy to change that? No. So you work with it; you have to work with it. But, then again, I didn't have the tools at FDA that I could work with when I was at NCI. At NCI I had a thing called the bypass budget, which enabled me to promulgate a strategic plan for the NCI along with a business plan for the NCI of how much money we should be investing in this kind of research or how much money we should be investing, or what programs we would like to bring forward and how much they would cost. And that bypass budget, which was for public

consumption, informed the entire community of policymakers, advocates, and taxpayers, and everyone else, what we wanted to do, how much it was going to cost, and what they would get in return. I don't have that opportunity at FDA.

At NCI, I had a National Cancer Advisory Board of individuals who I went to like a CEO goes to any Board and reports out on what our progress was, what our needs are, what our plans are, and they have the responsibility to and the authority to support and advocate for, and I have other program advisory boards like the Board of Scientific Advisors, the Board of Scientific Counselors. The FDA has a lot of advisory committees, but they were all down dealing with specific micro issues of decisions about an approval or advice on a particular scientific question. There is no macro opportunity to create these long-term strategic opportunities. And over a period of time, you see the consequences of that in that you see an agency that, by virtue of the fact it had no advocacy, by virtue of the fact it had no opportunity to develop a strategic agenda with a business plan commensurate with it, with the ability to measure and define and determine outcomes along the way and be held accountable for it, it was an agency languishing in a system where demands kept getting heaped on it, but the need to create what was going to be

necessary or required not just to meet the demands, but, more importantly, be able to be prepared for the opportunities. And that's why, during that six-month period of time, although I love the NCI and my lifelong passion had been around cancer, and I had set a goal, and a lot of people had bought into that goal; and I felt like to leave NCI and to abandon that goal was in some ways felt like, to me, like I was leaving a patient that I had agreed to take care of and who now I was suddenly no longer going to be taking care of, and that was painful for me; that was emotionally difficult for me.

But someone asked me the question, deep down in your heart of hearts, with regard to NCI and with regard to FDA, where do you think you could make the most difference, where do you think you're needed the most? And it was clear that the answer to that question was FDA, that FDA's mission was so critical, not just to cancer but to everybody, because it was not just cancer, it was everything, and that the NCI had great support and great leadership -- I've already alluded to the budget. It was the biggest of all the agencies, etc., etc. You know, I knew NCI was going to be fine. It may not quite be the same with me not being there driving that 2015 goal, but it wasn't going to fail.

With regard to FDA, with the problems it had gone through with regard to commissioners and temporary appointments and difficulty getting confirmed because of all the politics and Plan B and everything else that was floating around, that if I was to say, and if there was the part of me that hopes to make a heroic difference, that that was where I should be.

JS: You know, it's interesting, not so much when you were appointed as the Acting Commissioner, but when you were nominated to be the Commissioner, all the things that you faced. You mentioned the holds that were placed on your nomination over Plan B; over imported drugs, cheaper imported drugs; over why is RU486 still there, that's a problem. You had people within the agency saying they felt that there were political involvements in the decisions that were being made.

AvE: Yeah.

JS: All these things were coming up at the time. I mean, did you wonder what on earth you'd gotten yourself into at this point? Because surely when you came on as NCI Director, I can't imagine it was anything even approaching the scale of the politics involved as when you were nominated to be Commissioner?

AvE: You know, the truth of the matter is I had friends, mentors, inside Washington who were telling me privately, “Are you crazy? You don’t want to do this. This is the second worst job in Washington. You don’t want to do this. NCI, that’s your life. There’s no failure at NIH, at NCI.” You never heard of a hearing that was being held because nobody discovered a gene. There’s only success. There was always more money, except maybe now, but then there was always more money. And there was always the celebration of all the good things that research was creating. At FDA, all I saw was nobody ever celebrated the FDA for all the good things they were doing. They just wanted to beat on FDA for something that didn’t go right years later after a decision.

But the truth of the matter is, as I said, when you were there for a period -- I’ve often used this quote in talks -- it’s hard to love the FDA from the outside. Everybody hates it from the outside. But once you’re inside the FDA, it’s impossible not to love it; it’s impossible not to love it. I could not walk away from that agency. I would never have been able to have looked myself in the mirror if I had left you all in that lurch, having come and seen what I saw, knowing how bad the situation, would be like walking past someone in the street who’d

gotten hit by a car. I could never do that. I mean, I could never have left you, abandoned that agency. And so for the three years that I knew the rest of my time in the Administration, I made the commitment I'd stick it out to the very end, and I would do whatever I could. And we were going to get better.

And I had to be confirmed. Without a confirmation, I would have never had the authority or the leverage to provide the kind of leadership they needed. I had to do whatever I needed to do to get the resources.

And then we had to start building programs. We had to start solving our problems. FDA Beyond Our Borders was a piece of that; the fellowship, the Commissioner's Fellowship Program was critically important to that. I mean, to be able to bring the best and brightest into the agency. The creation of the Reagan-Udall Foundation was a part of that, and God bless Senator Kennedy. I mean, I may have had difficult times on the Hill, but I would tell you that we also had great supporters on the Hill on both sides of the aisle, great supporters. And I would put him up there. There are many, many others. You mentioned one name; you should mention lots of names, and there clearly were many names. But I mention his because he's no longer with us. And he was a champion of that agency before I got

there, and even though we may have been on different political -- I was part of a Republican administration -- he could not have been more supportive and of greater help. And it was because of people like him and others on the Hill and within the administration. I mean, Secretary Leavitt and Secretary Thompson were both extremely committed to the support of the FDA, but they were, you know, FDA was just one of their children. I mean, they had others, and they had an agenda with Medicare and prescription drug benefits and the whole variety of things they had to worry about.

JS: But you brought something up, a couple of things. One is globalization. I want to talk a bit about that. But the other thing, to kind of continue what you were talking about, the budget process and the support -- and this is farther down the line, this is about 2008 or so, if I'm right -- but there came a point where you did something that was a little unprecedented. I'm not sure how this played out, and that was actually requesting of Congress more money than the President's budget called for ~~for~~ the agency. If I'm right, about $250, $300 million, and that was in part, I think, because of this huge influx of imported products, drugs, foods, and so on. There was the reality of what the marketplace is like in this

country, that we're relying on these imported products and not fully dealing with this without the added funds.

How did that work out? How does one, as an agency, do something like that, and how was that received? Because Congress certainly seemed to agree with you that the agency needed more money, unless the reports I've read are not reporting this correctly.

AvE: Well, I mean, it's -- I don't know how to best put this for you. You know, difficult times require difficult decisions, and the budget cycles were such that the agency really could not survive just hoping that the next budget cycle would bring an increase. We were on the verge of catastrophic failure, and the one opportunity for there to be an intervention into that, the only intervention, was the Supplemental War Bill. So here was a bill that was going to fund our military activity as a reflection -- again, it's been years, so I don't remember exactly all the words -- but the bill was a bill that was fashioned by members of Congress that would provide funds for our defense. The FDA's role was absolutely critical in our defense, and that was, that's another part of the catastrophic-failure story.

When I first arrived and we were deeply immersed in the whole area of bioterrorism, and there was all of the

efforts going on about also a pandemic, and great fears about H5N1 avian influenza, and Tony Fauci and NIAID was geared up with all the vaccine development, and I arrived, and the only bit of money that had trickled down from that appropriation to the FDA went to CBER around vaccines, but no one had at any point in time recognized that FDA needed money in CFSAN because they would be responsible for dead bird carcasses; and CDRH needed money because they had to be responsible for respirators and masks; and CDER needed money because they were going to do the antivirals. So it was more than just CBER. But the FDA had been neglected, again. And here was another bill coming up that was going to infuse funds, and it was about defense, and if we were going to defend our country against bioterrorism and everything else, I mean, FDA was going to have to be front and center in that kind of thing. As a matter of fact, we were the only ones that had put together a task force, and we were the ones who wrote the first strategic plan, even with the Department of HHS for countermeasures.

So, at any rate, the War Supplemental created an opportunity, a pathway for a supplemental appropriation to the FDA. It was a supplemental appropriation for a war effort on which a piece or a part could come to FDA. And the issue was, in a response to Congress, I'd received a

letter from Senator Specter specifically asking me, what do you need, and what would you do with the money, and I responded to that. And that created a process that ultimately led to that supplemental infusion.

JS: So these funds did not come out of the appropriation for the Department?

AvE: No.

JS: These were funds from an entirely different pot.

AvE: Right, entirely different pot. But it was extraordinary to . . . There was -- it was an interesting process; I'll leave it at that.

JS: But on the issue of globalization, that was part of what was driving this need for funds. Is that right?

AvE: Well, the globalization issue was coming home. The data and everything else was all there. I mean, there was no question about that. There was no such thing as made in America. I mean, everything is assembled somewhere, parts and pieces coming from all over, and we had seen for a long time excipients and active pharmaceutical ingredients were coming from beyond our borders.

What precipitated that and where we had the opportunity to, again, strategically capitalize on a challenge and turn it into an opportunity, was the melamine

in pet food. And we reacted to that in a very powerful and strong way, but in a very collegial and collaborative kind of way with our counterparts in China. Our first experience was a very difficult one, even trying to get our inspectors into China. But what that did was it created an enormous amount of public awareness. We got more phone calls about cats and dogs in one month than we had the entire previous year. We had a lot of attention on the part of Congress.

And there were other issues that were developing with regard to imports coming from China, and there's tires problems, and that got the administration's attention of this being a real issue with regard to our trade relationships with China, and it came in the context of the fact that China and the United States had had an ongoing dialogue called the Strategic Economic Dialogue between China and the United States that was at Cabinet level. The Vice Premier of China and Secretary of the Treasury Mr. Paulson were leading that. And because FDA helped so significantly in imports and products coming from China, the agency was included in the dialogue. So suddenly there was an opportunity. The stars were aligning in a way that we could really direct attention to this in a way we could not before. And so working with Secretary Leavitt, who

President Bush put in charge of the Import Safety Working Group, FDA played a critical role in that, and he and I went around the country and visited ports and went into grocery stores, and we spent a lot of time working with China and India and other places exporting to the USA. And what was clear was that you could no longer sit at the ports and hope to inspect problems out. It was just . . .

JS: The influx of products was just overwhelming, wasn't it?

AvE: Yeah. It was ridiculous. I mean, I sat at the port in Seattle and watched container ships come in, and this is a joke. We were opening some of them up and looking at cookies that were in boxes. I mean, there was just no way. And you'd go to the ports and the import lines were coming in almost as fast as you could read them. We were working on strategies to do risk-adjusted inspections and things of that, so we were working collaboratively with Customs and Border Protection to sort of start to figure out ways to share resources, because they were obviously in a resource growth mode, and we wanted to surf that wave as well.

But the real opportunities were clear that if we were going to protect our own interest, the best way to do that was to have those who were producing products take

responsibility for their quality, not simply have that resting with us. And to do that, you had to be there; you had to engage with them; you had to be present with them; and it was clear that the only way to do that was to get beyond our borders. And CDC had successfully done that. CDC had CDC's personnel stationed at various countries around the world, and so I wanted to emulate that. And we conceptualized the FDA Beyond Our Borders realizing that we already had a great relationship with Europe, but we could expand and build on that. We needed to be establishing a relationship with China. India had already asked me early on for help and support as they were formulating their regulatory infrastructure, so we, rather than being consultants to them on an as-you-wish basis, we were proposing to them that we set up an FDA presence in India and be able to work directly with them, and so I spent time in India visiting with the officials . . .

And then Latin America was such a big part of our produce imports, and they were having a growing activity in pharmaceuticals. So it was clear that we wanted to be in Europe and China and India and Latin and Central America. And then I really felt the Middle East was critically important. And Jordan and Israel would be two great opportunities for us to have a presence in the Middle East,

so much going on, particularly in generic drugs. So that got formulated and became a real signature initiative, as were other efforts like the Commissioner's Fellowship Program and then others.

JS: So there were, under your tenure, then, there were three offices?

AvE: We got them all opened except the Middle East. We didn't get to do that -- we were close, and then Gaza tensions broke out and that derailed some of our relationships as far as the State Department was concerned.

JS: This is a very different way of doing things from the historical setup within Regulatory Affairs in FDA, where we had a couple hundred district offices, resident posts, and so on, set up domestically, and, as you said, import operations. But this is a very different way of doing things. Were there hiccups along the way of getting these offices staffed or getting people to spend time in China and India?

AvE: No. Actually, surprisingly, it was amazing to see the positive response. There were many senior people within the agency who were looking for something new and fresh and exciting for the next step in their career..

I mean, again, going back to the demographics, it was a blessing and a curse, the fact that we had so many people

who, like yourself, had been at FDA for 20, 25 years, and I don't think we ever did a very good job at FDA because of the constraints of resources and stuff like that in terms of career development. And in addition to the Commissioner's Fellowship Program, one of the other things that lagged and I didn't get time to really complete, but I still feel extremely strongly about, is career development and the need for sabbaticals and the need to be able to bring people into the institution for temporary periods of time, be they from academia or industry.

And I always believed, with faculty when I was at M.D. Anderson, that you had a zone of responsibility, a job we expected you to do, and that we needed you to carry out every day. But beyond that core responsibility, you should have a growth zone, and that was a zone where you were reaching for something. And I don't care how you did that. You could be taking a course, you could be collaborating with somebody to kind of move your research into a different area, whatever. But you should be growing; the organization should be growing; you should be learning, because if you're doing the same thing the same way next year that you did this year, then I've failed you, and you're failing the organization because you're not growing.

We were not doing a good job of having our senior FDA personnel grow, and primarily they were saddled with having to do the job they had, just moving that freight. They had no time, they had no freedom, they had no energy left over to take on or to push their own horizons a little bit, and that's got to change.

And the idea of bringing in the Fellows, the plan was, by this point, I had expected we would have 2,000 Fellows at FDA, a thousand a year turning over the way that it was structured, as I expected the churn for us was to keep 200 every year. We could keep 200 of the best and brightest in that Fellowship class as FDA career people and add 200, who had already done two years of fellowship in the agency, so they weren't starting at ground zero. They were ready to hit the ground running.

JS: How many did we start out with?

AvE: I think we started out with 50 or something like that, but we could ramp it up. And the people said 2,000 was too ambitious or too big a number, but if you projected, as I did, what did I think the workforce should be at FDA, I anticipated, to really deal with our burden, we needed 15,000 people, and we were 9,000, and I think when I left we got up to 12,000. I don't know where you are now.

JS: I think we're at 14,000.

AvE: You're at 14,000? I was looking at 15,000. Now, if you take 15,000, then 2,000 fellows fits if you start out with the premise that you're in the intellectual capital and information management business, I mean, everything you do is done between your ears, for the most part, with tools, the computer, or whatever. But this is an intellectually rich business because you're not making a widget or repairing a carburetor or something. Two thousand, to invest in 2,000 people when you've got a 15,000-people core, is just about right to keep that growth, keep that going, because you're going to lose to attrition. You know, you can expect to lose 10 percent of your workforce every year, if not a little bit more.

And FDA I calculated as being higher than that simply because of the demographics of average age of 47 and 30 percent eligible for retirement. So you have to find a way to be able to supplement, and you can't go out and hire that number of people. That's a lot of hires. And plus, when you hire them in, they're starting at ground zero.

The other idea behind that which I got, we would be returning back to academic and industry 800 people a year who understood and knew how FDA worked, and if you think about how that could streamline the ability, for example,

of small biotechs and things to be doing their development, which eventually would mean that the applications coming to FDA would be far more sophisticated, far better developed, far better, far better done, and when there were questions or issues, they could have been addressed far more easily at the front end so everything works better. It will even make the burden of the work lighter because it's going to be better applications coming your way because smarter people are putting them together.

JS: Which makes our job a little bit easier as regulators.

AvE: And that's a dream and other dreams, like the Commissioner's Fellowship Program, should not languish. That still needs to get done.

Other needed changes were clear to me when I first got there such as how fragmented you all were. There was a chart up in my office in Parklawn of where all the various offices at FDA were spread around the Washington, D.C. area. That was pathetic. And there was the plan for the White Oak campus. So I jumped into White Oak with both feet and both arms, developed a very close relationship with the Commissioner at the GSA, David Winstead, and we teamed up and we put our shoulders together to get White

Oak done. And, again, we had a lot of support from Congress and the community like LabQuest.

JS: The FDA Alliance I think formed during your tenure, did they not, a group of former FDA employees, I think?

AvE: The FDA Alliance was started, or the FDA Advocacy Group was started first by Secretary Thompson, and then the Alliance spun off of that with the focus of continuing to try to drive support for funding for the FDA.

JS: Okay. Were they successful?

AvE: You know, coming from NCI, I mean, I had more advocacy groups than I knew what to do with in many ways, and there wasn't anything that you could need or want at the NCI that somebody was not going to advocate for. You got to FDA, and zero, nada, no one. There were no cheerleaders for FDA. There were a couple of individuals, but no organizations that made FDA their focus. The Alliance for a Stronger FDA was a great contribution.

Now, as an individual, Ellen Siegel was always supportive of the FDA by virtue of her commitment to cancer, and she had been involved in ODAC and its development and things of that sort, but her Friends for Cancer Research was not an FDA-oriented advocacy group. It is now, and she spends a lot of time with FDA folks now

engaged in things. Now you're seeing advocacy groups begin to recognize that their agenda has to include a modern, strong, well-resourced FDA. In response, the FDA has to change. It has to modernize. It was the gold standard of the 20th century. But what was obvious at that 2006 birthday was that the world around the FDA had radically changed and was radically changing, and will continue to radically change, but the FDA was not changing. And a lot of that had to do with the fact that it was so resource-constrained; it had no energy to change; it had no freedom to change; it had no elasticity; it had no growth zone.

JS: What kind of change are you referring to?

AvE: Well, first of all, there needs to be change in both capacity and capability. Okay? So we've already talked a lot about capacity-building. Capability-building is equally important.

I used the example earlier about the power of regenerative medicine based on two things: one, the evolution of stem-cell biology, and then the availability of enabling technologies and material sciences. If you think ahead as to what will the future look like with regard to medical product development, the historical model and the organizational structure has been primarily focused on the development of components, so we have drug companies

that make drugs and we have a Center that regulates drugs; we have companies that make biologics and we have a Center that regulates biologics; we have companies that make devices and we have a Center that regulates devices. Those are components, and those components have to be absolutely the best that they can be. But what complex diseases are telling us that no single component is ever likely to be the entire solution to the problem; that these complex diseases, be they cancer or Alzheimer's or whatever, are going to require solutions that, by their very nature, will involve the integrated, interoperable combination of components. So think laptop, think your computer. Intel makes a phenomenal microprocessor that does all kinds of whiz-bang things faster than the speed of light or whatever. Great! And Cisco makes hard drives that are phenomenal, and Microsoft has great software, blah-blah-blah. I wouldn't give you two cents for any of them. They're absolutely worthless to me, useless to me. Andy Grove is a good friend. I have no interest in his microprocessor, until Andy Grove puts his microprocessor together with Bill Gates' software and somebody else's CD-ROM and somebody else's hard drive and gives me a laptop. Oh, that has value for me. I can do word processing on

that, I can do emails on that. That I'll pay for, that I need.

We need for Alzheimer's, cancer, and all the rest, the integration of these components, integrated, interoperable solutions. It's not good enough that they are just great components. They actually have to work together in a way that produces the desired outcome.

So suddenly we see that across these domains of drug makers, biologic makers, device makers, software makers, whatever, there needs to be integration, and across these regulatory components there needs to be integration -- not coordination, not combination products. You know how we regulate combination products. There's an office that says there's a little bit of this and there's a little bit of that. Do I send it down that pathway, or do I send it down that pathway? That's got to go away. That's 20th century. Twenty-first century is we've cut horizontally across all of these domains. Do we destroy them? No. They're intact. But we integrate horizontally across them in a meaningful kind of way. Cancer centers learned to do that a long time ago because you couldn't solve breast cancer as a surgeon or as a radiation therapist or as a medical oncologist. The only way you can solve breast cancer is

when you put all three of them together and you add the other pieces, the pathologist and all the other elements.

So the mindset that I had coming from the NCI and from my background at M.D. Anderson is, this agency needs horizontal integration. White Oak was redesigned to do just that. We got together and stopped building silos, which is what it was planned to do. It was geographically taking silos and just putting them all on one campus. Wrong. It had to be built in a way that there was infrastructure integration. We even drove down to details like where you would eat and where you would hang out and force you to have to go and interact with people from other Centers. It's the Harvard Business School model of the common water fountain. I wanted IT systems and data centers that were centralized and enabled cross-cutting access to the data. It makes no sense to have data in the silos that one silo can't get to in the other silo; it makes no sense at all, on and on and on and on. So there is capacity and capability, capability changes that are going to require structural change, that are going to require functional change, that are going to require cultural change. There needs to be process improvement.

I sat in the Office of the Commissioner. I have multiple Centers and Divisions all making regulatory decisions . . .

TAPE 2, SIDE A

AvE: There is no way, at least there wasn’t when I was there, no way for me to look across that agency and evaluate now regulatory decisions are being made in every part of this agency. I need to know the process that’s being followed in those decisions. I want to know that there’s a standard for those processes. And when there’s a deviation from that standard, I want to be able to understand that deviation so that we can get to the root cause and reduce variance around the mean, because that’s the principle of improving quality and reducing waste.

There’s a process for doing a clinical trial. Okay? You map that process out. You look at the metrics associated with that process. You realize the steps that go into that. Oh, there’s a step where you have to get the protocol approved by the IRB, and depending upon what goes on in that cycle could influence and determine what the outcome of that cycle.

User fees were looking at the total time that it takes to get from point A to point B. That's not the way you do it. You look at what goes on in getting from point A to point B, and you map and you track and you follow and you constantly improve. It's called continuous quality improvement. There's no mechanism for doing that; there was no mechanism for doing that within the agency, across the agency. There may have been pockets where people were trying to get a grip on that and trying to be able to manage that, but there's no way of looking at it by the Commissioner. And if you're going to start integrating, then you're going to have to start being able to understand those processes, because they're going to be now superimposed or connected. Okay? Because the application for that artificial or that regenerated kidney comes in here; it's going to have to go out here. FDA is going to have to not only know that the component is good. Does the genetically modified stem cell meet our expectations? Does the matrix meet our expectations? Do the growth factors that are nano-encapsulated meet our standards? Oh, and then, by the way, when I put all three of these together, can they work and are they integrated and interoperable in a way that the whole thing is doing good and not blowing up? How are we going to do that? You guys are having a

difficult time just figuring out how to put a diagnostic and a therapeutic together. Right? How long have you been at that?

I've been out of that agency now for years. That was something we talked about when I arrived, and I brought all the Center Directors . . . How many years is it going to take? There are people suffering and dying out there. A regenerated kidney that delayed, just delayed, transplant or dialysis for a year would drop the cost of healthcare by hundreds of millions, if not billions, of dollars worldwide. This is not an intellectual exercise; this is not a task. This is a mission.

JS: One of the things that we depend on in decision-making is evidence. Right? So, one of the ways that you looked at what the FDA in the 21st century could do is maybe reexamining what Phase III trials are.

AvE: Absolutely.

JS: So, a Phase III trial obviously is something that we've ratcheted up. So, how do you revisit the Phase III trial and yet still have the sort of scientific confidence so that you don't have to go to this issue of just do no harm, but you have to have evidence so you can make an educated scientific decision?

AvE: Look, it's not easy, and I'm not saying, so a wahoo like me comes along from South Philly, waves a magic wand, and we live in never-never land, you know. It's hard, and there's a long conversation around how you manage change.

You have to morph from where you are to where you need to be, but you have to know where it is you want to be, if they'll agree to that, then you strategically start changing the parts and pieces to get you there without destabilizing.

How do you change a bridge? You can blow it up and build a new one; you can build one like you did on 295, build one alongside of it, and then one day move over, move the traffic over; or you can morph.

You can't blow up the regulatory process and build a new one. You've got to keep going. And you don't have the resources and the luxury of building an alternative one, although that's been suggested as far as disruptive innovation, to take it outside. I don't want to see that. So morph it, but morph it strategically, which means you have to understand how it works and you have to be willing to give up the way you do business. Why are you doing business this way? Where did it come from? Go back and look at it. It's a fabrication. The Phase I, Phase II,

Phase III prospective randomized trial with P values is a fabrication. It's a statistical fabrication to try to reduce bias, because you didn't know; you have no clue as to all the variables determining the outcome. So you try to blank out all the variables, except one by randomization, which hopefully, statistically, gets you to the point where all else is evenly distributed. No, that never happens in the real world, but we get relatively close, especially if we have big, big, big, big, big, big, big trials, which you can't do anymore. But that's what we needed to do in the past because it's all we had.

Now, if I can take the cover off, there's two populations, and unblind you and say I can tell you the difference between that person and that person and that person and that person because I have this new information, this data about their genetic defects in their tumor or whatever you want, whoa, maybe I don't have to be blind anymore, do I. Okay? So you've got to really start conceptually with the fact that I'm willing to give up the traditional if you can give me the same degree of comfort in the new model that I had in the old model because this is just a construct to enable me to be confident and comfortable in my regulatory decision, so let's create a different construct.

What would it take to give me confidence in the new construct? Well, I need new tools. What are they? Well, I need to be able to discern one population from another. Okay, let's agree to that. What's that called, a biomarker? Oh, biomarkers. We've got to get serious about them, don't we. Okay. What else do I need to know? I need to be able to get data, track it. Okay. So that means a new way of designing and creating infrastructure. Do we have those tools now? Yeah. Everybody's walking around with them strapped to their belt. I mean, I could monitor your pacemaker wirelessly anytime I want to. So, how do we introduce those tools into this new system? What tools make sense? Which ones don't make sense? Which are essential and strategic? Let's start morphing.

I write about this. I hope people are smart enough to realize I'm not talking about blowing up the entire clinical trials infrastructure and suddenly migrating to Phase IV observation trials. What I'm trying to get people to do is to open their eyes to the fact there's a new way you can do this. You don't have to be mindlessly wedded to Phase III as the only pathway to being able to put a drug out on the market and allow people to use it. A Phase IV trial, observational trials, given these new tools, can give you as much comfort, that is information, as does the

traditional way you've done it before. But let's get together and wise, smart people, people who are a lot smarter than I am, with an open mind and a willingness to change, and not absolutely embedded in the past, figure out how we could do that.

That's what I'm trying to stimulate, and sometimes that makes people angry, and sometimes people think I'm criticizing the agency. I've never once criticized the FDA. That doesn't mean I'm not critical of the FDA. But, then again, I'm critical of myself. I never did an operation in my entire life, no matter how good it turned out, whether I walked out of that operating room and said to myself, "There are only five people in the world that could have ever done that," without sitting down and saying, "Okay, hotshot, how could you have done that even better? How are you going to do it even better the next time?" FDA is great; it's phenomenal; it's unbelievable, and I'm not criticizing FDA when I say, "Okay, but let's be a little critical. How could we do it even better?"

JS: As you know, FDA has a pretty thick skin. Whether someone is criticizing or being critical, it's an agency that can change and has changed. Sometimes it takes it a while.

AvE: It has to change; it has to change faster because the world is changing faster. It has to. And that requires taking some risks. And, again, maybe I'm a product of my background. I'm a surgeon, and surgeons are trained to be able to make decisions with absolutely less-than-perfect information because to not make the decision does harm. If you're taught at the very beginning you'll never be 100 percent sure that child has appendicitis, you have to get as close to 100 percent as you can before you pick up that knife, and it may be 95 percent, maybe 97 percent. It ain't ever going to be 100 percent. And there will be a time when you will have picked up that knife and you will have done that operation, and the pathologist is going to tell you it's a normal appendix. And that you're going to live with because the other 97 you took out were not. But you took out one that was normal.

But if you did not do that, and if you waited until you were absolutely 100 percent sure, every appendix you've taken out would have acute appendicitis. But there will be two or three of your patients dead because they had peritonitis from a ruptured appendix. So you have to look at the downside of not making a decision, of not going faster.

One of the things that’s never been done is there’s never been a really good study of what is the harm for the FDA not having approved a drug? What is the harm of taking too long? How many lives got lost because this decision eked out longer and longer and longer so that we could be comfortable? Confident, yes; you should always be confident in your decision. But confident doesn’t necessarily mean you’re comfortable.

JS: I know you have to catch a plane.

AvE: I’ve got to catch a plane.

JS: And I do appreciate your taking the time.

AvE: I’ll do it again.

JS: Well, we might need to follow-up.

END OF INTERVIEW