History

of the

U.S. Food and Drug Administration

Interviewee: **Russell G. Katz, M.D.**

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

Date: **June 21, 2013**

Place: **Silver Spring, MD**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TOPIC OF INTERVIEW: History of the Food and Drug Administration

LOCATION OF INTERVIEW: FDA White Oak Campus

DATE OF INTERVIEW: June 21, 2013

INTERVIEWER(S): John P. Swann, Ph.D.

INTERVIEWEE: Russell G. Katz, MD

FDA SERVICE DATES: March 1983 to June 2013

TITLE AND ORGANIZATION: Director, Division of Neurology Products
Center for Drug Evaluation and Research

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Russell G. Katz

June 14, 2013

TAPE 1, SIDE A

JS: This is an oral history with Dr. Russell G. Katz. It's 21 June, 2013. My name is John Swann, and the interview is taking place at the FDA campus in Silver Spring, Maryland.

So, Dr. Katz, first of all, thank you for joining us and participating in this oral history. I'm looking forward to hearing about your work here at the agency.

But first we want to start with your background before you came to FDA, where you grew up, what your early educational interests were, and how you sort of came to arrive at those, and even the people who had an early influence on your decisions and, for example, in going into medicine generally and neurology specifically.

RGK: Okay. I was born in the Bronx, and I moved on my fourth birthday to Queens, so I grew up in Queens and went to New York City schools, and I went to college at Queens College, which is a branch of the City University of New York, a public college, which was about four blocks from my house, so I lived at home during college. I had to

pass my elementary school to go to college, and I had to get crossed by the crossing guard, the sixth grade crossing guard, because I was with all the kids going to elementary school.

So I went to college there, and I guess I always sort of assumed from, let's say, early high school, junior high school, that I would be a math teacher. I loved math. But somewhere in my high school life I thought about the possibility of going to medical school. And, quite honestly, I didn't know anybody in medicine. I, of course, went to the doctor from time to time, but I had no relatives. My father was a working-class man, and my mother didn't work outside the house, and no one in my family had been to college except my brother, who's a year and a half older than I am, and he was in college. I think, honestly, I thought that medicine would be a fascinating profession, mostly I think because of television, quite frankly. There were a lot of doctor shows on TV at the time, and *Dr. Kildare*, you might remember, and *Medical Center*, and they were all good-looking and very accomplished, and they were saving people's lives, and that struck me as being something that was worthwhile doing. So I think around my senior year in

high school somewhere, I decided that's what I would try to do.

And so I went to college. I started out majoring in chemistry, and once I got to the point where I had to do a six-hour lab, and you walk in at noon and it was sunny, and come out, it was freezing cold and pitch black, I said, "Chemistry isn't . . ."

JS: Organic, no doubt.

RGK: Well, physical chemistry and then organic, of course. That was the great dividing line between people who got into medical school and people who didn't. So I decided to switch my major to mathematics because I always did love math, and there were no papers to write or labs to do. It was a very easy major if you can do math well. So I enjoyed that very much.

And then I applied to medical school and I got into a few medical schools. Albert Einstein in the Bronx was where I wanted to go, and I was fortunate enough to get in there.

But my thought about going to medical school was that I would be a surgeon. There seemed to be no particular reason to become a doctor other than to become a surgeon. That seemed exciting and it seemed that you did real good for people in a very sort of immediate, tangible way. So I

went to medical school, and one of the first courses I took in medical school was taught by a surgeon. It was anatomy, and I was thrilled. I spent a lot of time in the anatomy lab, a lot of extra time in the anatomy lab. I smelled from formalin for about a year and a half. I couldn't get that out of my clothes. But it was great; I loved it.

And one of the other first courses I took was neurobiology, which was fascinating. I loved that.

But nonetheless, I still thought that I would be a general surgeon, and throughout medical school that was my plan, and I did a general surgical internship at the Einstein Hospital in the Bronx. And it wasn't nearly as exciting as I thought it would be or as interesting as I thought it would be, so I remembered that I always loved neurology, so I said, well, maybe I should be a neurosurgeon. So I switched into the neurosurgery department. I did two years of a neurosurgery residency and, quite frankly, that was more interesting, but the people were very difficult to deal with in my institution, the neurosurgeons. There are stereotypes about neurosurgeons, and they all met them, very difficult personalities, very big egos. But I learned later that that doesn't have to be true. But in my institution, I found it difficult to really spend a lot of time with those

people, so I switched to neurology because I was no longer enamored of surgery. I still liked neurology, but neurosurgery wasn't for me, so I finished two years of neurology residency.

And then I figured I would work in the Bronx for the rest of my life . . .

JS: In the practice of medicine.

RGK: Well, I figured I would work at the hospital that I trained at and be on the faculty. I trained mostly at a city hospital, a public hospital in the Bronx which was affiliated with Einstein. So that was, that seemed to be something that seemed like a worthwhile thing to do.

But I met a woman who ultimately turned out to be my wife, but she got into law school down here in Washington, D.C., when I finished my residency. She applied to law school at one place and she got in there, so she lived in the Bronx for several years because of me, so we moved down to Washington, D.C. to live. She was going to law school.

JS: Now, when you moved down, did you have any idea in advance what you might be doing?

RGK: I had no idea. I figured I would look around to get a clinical job because that's what I was trained to do. Although I have to say that towards the end of my residency in New York, I began to become more interested in sort of

the intersection between medicine and politics with the society, larger issues related to health as opposed to individual patient care. What I was trained to do was individual patient care; that's what a residency is. But I began to become more interested in sort of how does healthcare fit in, taking care of one person versus some social act or political act that could affect large numbers of people's health.

JS: Did something in particular lead you in that direction?

RGK: I think just my sort of political awareness. I think it was more just becoming more interested in politics, and my wife -- we were not married at that point, although we got married just before we moved down here -- was very political, in fact ultimately, after we got down here, she was elected to the Maryland state legislature. She was there for 12 years after law school. So she was political, and that was actually one thing we had in common, was our politics. So I think it was mostly that sort of thinking about, oh, sure, you can take care of one person, but a number of what we define as medical illnesses really have their origin in social conditions and that sort of thing.

But mainly when I came down here, I was looking for a job. That was sort of where my thinking was, but I came here and I went looking for clinical jobs, hospitals, practices. There are many training programs here locally in D.C., and if somebody wanted to get a young neurologist, they didn't have to take somebody from New York who they didn't know. They had a large choice amongst people that they probably knew locally. So I wasn't getting any bites.

And, in fact, just to make some money, I took a job for several companies doing insurance physicals, so I would travel around the metro area, D.C., Virginia, doing insurance physicals, but I made enough money to pay for my carfare. It was horrible; it was horrible.

JS: [laughs]

RGK: And a friend of mine, who I knew actually from junior high school and college and medical school -- we went together -- saw an ad in the *New England Journal* for a medical reviewer for what was called then the Division of Neuropharmacologoical Drug Problems. So I wrote a letter in to Paul Leber, who was the Division Director here at the time. And so I wrote him a letter, and he called my house and, while I was out doing one of these insurance physicals, he spoke to my wife, who happened to be home. And I don't really know exactly what transpired in the

conversation, but I had the sense when I showed up for an interview, it was sort of a pro forma thing. I think she got me the job. She must have either been desperate herself or saw how desperate I was to get a job. But, in any event, it must have been a very positive phone call, because when I came -- I could be wrong about this -- but it seemed like he was favorably disposed to me already, and obviously it was not because of anything I had done; we had just met.

So anyway, I was hired. So this was March 1983.

JS: So, what sort of an impression did you have of FDA at the time you sent in your application?

RGK: Well, first of all, well, at the time I sent in the application, I had no impression of the FDA. In fact, I'm not sure I could have told you what those initials stood for. I went to medical school, I graduated in 1977 and I finished my residency in 1982, so that's the time period we're talking about. You never heard anything about FDA. There was nothing in medical school or training about FDA or drug approval or how that worked. You just knew that the drugs you had available to you were FDA approved, but that meant essentially nothing, to me anyway, and I'm sure it meant nothing to my colleagues.

JS: It was *Good Housekeeping* approved.

RGK: Right, right. I had no idea, exactly. There was no, I'll say there was no understanding about the process at all. That was true for me personally, and I'm quite sure that was true for everybody else, too, unless there were some people on the faculty doing studies, which I did not know about at the time. It's possible that's true. But nobody talked about the FDA. I knew nothing about the FDA. To me, when I applied for the job, the main thing was it was a job, and I knew that it was sort of a public health job, which, again, I had been becoming more interested in. But again, to be honest, it was a job, and I was happy to apply for a job, and I was ecstatic to get a job, but no knowledge about the FDA whatsoever.

JS: So, what was that transition like? Granted, you wanted a position, but that transition from the last position you had was as a resident in neurology at Albert Einstein to being a Medical Officer at FDA, that must have been an interesting one.

RGK: Well, it was a 180-degree transition. First of all, I learned quickly, well, many things. I learned quickly that what I had trained to do had very little to do with what I was expected to be able to do here. I mean, it's important to have a background in neurology, but, obviously, this job is not a clinical job, it's not the

kind of thing I trained for or almost anybody trains for, I think. It was an office job, which I had never had; it was a desk job, in effect, which I had never had; it was a job that involved a great deal of writing, which I had not done before. So it really was in some senses very little related to what I had been doing and what I had been trained to do, so it was a completely different job requiring different skills, very different skills, the acquisition of new skills, which I knew very little about. And also, it involved a radical rethinking of who you were professionally, because you train as a physician, a clinical physician. Everybody knows what a physician does. They are held, for better or for worse, in relatively high esteem. I don't know if that's still true, but it was true then. Everybody knows what a doctor is. Everybody goes to the doctor. Everybody knows what a doctor does. It's a prestigious job and title.

And then you come to the FDA. Nobody knows what you're doing. Your previous colleagues, your family, they expect you to be, to do what a physician does. And then you come here and you're an office worker or a bureaucrat or whatever you're called.

So it involves really sort of rethinking your whole self-perception. You know, before you were a doctor, and

here you were a doctor but you weren't doing anything that you expected to do or that anybody you know expected you to do. So I think that's an important thing. Those of us who have chosen to stay here, we're quite comfortable with that reordering of perception. But some people don't get over it, and for some people, it's a hard thing to do.

Now, I was young. I'd never practiced, so I hadn't been a physician very long. And, as I say, I was desperate for a job, so this didn't really have a, I mean, I had to come to terms with it, but I didn't really have a problem coming to terms with it. But it was an aspect of fitting in here, I think. You really do have to think of yourself differently.

JS: Some medical officers come here after getting their degree, going out and practicing medicine, and discover they don't like that. They don't like that at all.

RGK: Yeah.

JS: But this is something that they can relate to.

Now, you practiced medicine as a resident. Right?

RGK: Yeah.

JS: Did you, as a resident, did you ever participate in clinical trials?

RGK: No, no. I'm sure there were clinical trials ongoing. I say I'm sure. Again, this is late '70s, early '80s. I'm not sure, actually. There are certainly, at that institution they're doing trials now, but I was never aware. I was never a part of, that was never an expectation of the residency. It just wasn't, well, in my institution it was no part of the training. I guess maybe in some institutions even then, it could have been, but it was not. No, there was no discussion of it. As far as I know it wasn't happening. I knew nothing about clinical trials when I came here.

JS: Now, when you arrived, I assume you got the usual battery of training.

RGK: Well, there wasn't a battery of training.

JS: There wasn't?

RGK: Well, there was no formal training. Now, of course, we have a very extensive syllabus of courses that new medical reviewers take and are required to go through sort of a staff college. There are many, many, many courses here now, in all aspects of, I think, in all aspects of drug development and even communicating with people. But when I came, as far as I know there was nothing. And they did require us to take a course in statistics, and that course was given at the NIH, so, like

one night a week. I guess it was a year-long course. I'd go down to the NIH, FAES, and they gave a course in, I guess, sort of elementary statistics, biostatistics. So I did that, and that's what people in my bureau did. So there were no courses here. In a very real sense, it was another residency, and it still is. Even though there are courses that people take now, like anything else, you learn the job by doing the job. So you really learn by doing.

And when I got here, it was a very, very, very different place than it is now, in every possible way. There were a number of people in the division who had been here a long time, and -- how can I say this -- it was not a stellar organization. Paul Leber was the division director, and he was brilliant, and everything I know about clinical trials, I learned from Paul. But the rest . . .

So, anyway, I became a Medical Officer, and then very shortly after that I became the Team Leader in Neurology, and I was more or less the team as well. And then we started to hire people all the time. And then a few years after that, I became the Deputy Director. But it was a lot of learning by doing; it was a lot of, as they say in surgery, see one, do one, teach one, and I learned everything from Paul. We got along very well. So I was promoted up the ranks to Deputy Director fairly quickly.

JS: When you arrived as a Medical Officer, before you became a group leader, were you assigned any particularly interesting drugs to review?

RGK: Well, yeah. I wouldn't say it was my very first investigational new drugs (IND's), but one of the first INDs I worked on turned out to be amongst the most interesting and instructive INDs that I ever worked on. It was a drug called, well, at the time it was called gamma-Vinyl GABA; now it's actually on the market. The brand name is Sabril.

Anyway, it's an epilepsy drug, and it was a drug that I believe at the time had already been approved in Europe. You know, in those days, everybody talked about drug lag, so these are drugs that are approved in Europe and still unapproved here 10 years later, the lag between when it's approved in Europe and approved here.

So it had been used and was a pretty effective drug, and it was under an IND, being developed, and it was in clinical trials, and then we learned that it caused a particular pathology in the brains of at least three animal species and maybe four animal species. And the way we think about problems, at least the way we here think about problems that you see in animal studies -- and we rely a great deal on animal toxiocology studies here; we always

have in this division -- the way we sort of react to what we see in animals is dependent on many things, but one of which is, is something happening to the animals that we can monitor for in people?

So, like some drugs cause liver injury, but usually it causes the liver enzymes to elevate in the blood. So we say, okay, we can give it to people and we can check their blood to see if their liver enzymes start to go up, and if they start to go up, we can stop the drug. But there are times where drugs cause pathologic lesions that we don't know how to monitor for. So this was causing what's called intramyelinic edema in the brains of at least three species, and this means around the nerves, portions of the nerve cell in the brain, there is this myelin sheath that's sort of like insulation people talk about. It's very critical for normal nerve function. And there were vacuoles, sort of holes between the layers of the myelin, in several species. We had never seen this before. It was extensive in the brains, and we had no idea what the consequences would be, and we had no idea how to monitor for it in people. The whole idea is to be able to monitor something so that if you catch it early enough, you can stop the drug and these pathologies won't occur. That's the ideal situation.

Well, we had no idea . . . These animals kind of looked normal, and the companies did all kinds of tests on them that they could do, like they did spinal-fluid tests. And they said, “Well, look, we did every test we could think of doing, and they’re all normal. So, really, yes, it’s true, the brains look kind of bad on slides, but the animals seem to be okay and all our tests seem to be normal, so there’s really nothing to worry about.”

And I learned then, I learned many, many things in that case, but one of the first things I learned is, it’s fine to do tests and it’s fine for them to be normal, but all that proves is that your tests are not sensitive to the problem, they’re not detecting the problem. So when sponsors say, “Well, look, sure, the brain is liquefying, but all our tests that we know of are normal,” that’s actually a bad thing, because you have no way to know if it’s happening. So I learned that principle, and that’s a principle that we still invoke all the time.

So we told that company they had to stop testing the drug in people until they could come up with a test that would be able to detect the onset of this problem early enough so that if you stopped the drug, it wouldn’t go on to be, you wouldn’t have bad findings in the brain. And it took the company about five years to come up with a test

that was able to, that, when it first became abnormal, they looked at the animal brains and they looked pretty good, so it was a very early sign . . . This test was able to detect something going wrong very, very early, before it was a full-blown problem. And if you stopped the drug, the animals did not go on to get these lesions in the brain. So that's the perfect kind of test to have. And we assumed that the same thing would be true for people. So we let them develop the drug as long as they would monitor people with this test so we could be sure that these things weren't happening in people, or we were confident -- we couldn't be sure because you can't do brain slices in people.

JS: Did we have a sense of how often this occurred?

RGK: Well, in animals it occurred quite frequently, and so, and it was also, I believe that was also my first Advisory Committee meeting, because we took this issue to the Advisory Committee. So I learned a great deal about how you think about problems that you see in animals with regard to what it means in people. I learned a great deal about what makes a test a useful test. And that was my first Advisory Committee. Of course we had many, many, many more over the 30 years, but that was my first

experience, more or less my first experience speaking in public.

But that's not entirely true. When I was a resident, there was a big strike of interns and residents in New York, and I was one of the strike leaders in my hospital, so I gave a lot of speeches, political speeches, at the time. I'm sure I'm on some list.

JS: Oh, you must have been a popular person in the hospital.

RGK: Yeah, yeah, right, yes. So it was a very interesting time, actually.

But the Advisory Committee was the first time I had more or less spoken about a scientific issue in public, so it was really an eye-opening experience. And those, the principles I learned there, I still apply them all the time here. And you still hear companies say, "Look, we did all the tests we can think of and they're normal, but, sure, there's pathology, but it doesn't matter." And it's still false reasoning and you still have to point this out to people. So it's, that's stood me in good stead, I would say. I learned a great deal.

And that drug is now approved, but it got approved many, many years later.

JS: Do we know now how frequently there are problems, or are there problems?

RGK: Well, that's an interesting story, because as far as we know, we don't think that problem that we saw at the beginning is really happening in people.

However, just before we were about to approve it, because we didn't see any major problems with this testing, this surveillance method, we learned of a completely different problem that we hadn't predicted from animal studies, and it turns out that is a real problem. We learned this from patients, reports from patients, and it turns out a completely different problem exists with that drug. It causes a constriction of the visual fields. This is a problem that doesn't really happen in the brain; it happens in the eye, completely unrelated as far as we know. And I don't believe we picked it up in animal studies. And so people get tunnel vision on this drug, and it seems to be more or less irreversible, and that kept it off the market for several years before we figured that out, and we still don't really know why it happens, but it does happen. And so the use of the drug is, in some sense, fairly restricted. You have to have visual testing periodically on this drug. And it's a bad thing, but people still can

see if their visual acuity isn't affected, but their peripheral vision is constricted.

JS: And that's not reversible.

RGK: It doesn't seem to be reversible. But the fact that that is approved, even given that problem that we know about, which is clearly real and it's not rare -- maybe up to 30 percent of people have this -- the fact that we approved that I think outlines a few major points. One is, it was approved with a risk evaluation and mitigation strategies (REMS), which is one of these post-marketing risk evaluation programs, so we were able to institute a program that we think makes it basically required for physicians to make sure patients' vision is tested periodically. And we hope that -- and this we don't know for a fact, but we hope that would allow people to detect this early. We think that's a good thing, and if it's happening, you can decide to stop the drug. So fashioning that REMS, which is very complicated, was a learning experience.

But it also embodies a larger principle, which,in neurology we tend to take very seriously, which is that the diseases we're treating are bad diseases. Refractory epilepsy is a very bad thing. It's life-threatening. And we tend to approve drugs even when there are significant

risks because the diseases are bad and we don't have a cure for any disease. So we think it's useful for people to have options even if there's bad toxicity.

There are occasions where we have said, "Now, this is too dangerous. No, we're not going to approve this," but those are rare.

JS: In this case, the risk-benefit ratio, even with the problems, falls out in favor of the drug's approval.

RGK: Well, we think so, yeah. And, again, we have this program in place which we hope would permit people to detect it early, if it's going to happen.

But, for example, it's also approved for a rare type of childhood epilepsy, sort of infant epilepsy, certain seizures that these infants get called infantile spasms, and it's useful in that disease. And that disease is also a very, very bad disease, and there weren't many treatments. There were some treatments for it, but not many.

Now, this program that we have in order to detect this problem early is very much dependent on patient cooperation. In order to have visual fields tested, your peripheral vision tested, it requires a considerable amount of attention and focus by the patient. First of all, the patient has to report to you can they see something in

their peripheral vision, and they have to be able to look straight ahead and see how much you can see to the side. So it requires a fair amount of participation by the patient.

Now, we approved this drug for infantile spasms. Clearly, infants cannot participate in this kind of program, and for all we know, we have no reason to believe that the visual problems don't occur in infants. We think they are likely to occur in infants, and we can't detect it. Nonetheless, we still approved it because infantile spasms is a very bad disease with not enough treatments available, and the fact that this visual problem is known, if you look at the label for this drug, it's a box warning and it has everything you could have in a label that shouts warning, warning, warning. So we hope that physicians who use it for infantile spasms, even though they're not required to do all this testing because they can't, are aware of the problem via labeling and will be prudent about it. And so if the infants aren't responding right away, which they should for spasms, the physician can say, "Well, look, they're not responding. This drug has a bad side effect; I'm going to stop it. So the very existence of labeling and the educational, in this case, purpose that it serves permits us to approve a drug for a bad disease even

if you can't prevent the bad thing, but you can inform people and they can make a decision as to whether they want to use it or not.

So I think, actually, just the existence of a requirement for a label lets us approve things that we might otherwise not approve, because we might think, well, it's too dangerous. But now we say yes, it's dangerous, but it's a bad disease and people are aware of it. People know about it, at least, and they can factor that into their decision about whether they want to continue to treat the patient or not. So it serves an educational purpose and, as I say, if we didn't have that, if we just approved drugs and they didn't have labels associated with them, people wouldn't have enough information to make an intelligent decision about treating.

JS: One would hope they're reading the label.

RGK: Well, hopefully they're reading the label. We know they don't always, but for a drug like this in the epilepsy community, it is very well known that this problem exists, that there is this REMS, and the only people who treat infantile spasms, because it's rare, we think anyway, are experts in the field. Your average physician out there, the average neurologist out there, is likely not to treat infantile spasms, usually a pediatric epileptologist,

certainly pediatric neurologist, and the whole epilepsy world, the whole neurology world, is very well aware of this problem with this drug. So we're pretty confident, in a case like that, people know about it. Even if they don't read the label, this issue is so prominent that they all know about it. They all know what the problems are.

In other cases, you're right. We don't know if they read the label, and you worry about that.

JS: Well, I wonder. And there must be cases that I'm sure you can recount where we are approving the drug that community knows well, but perhaps that particular product might be finding a use outside of that community.

RGK: Oh, definitely.

JS: Obviously, an off-label type use, and that would cause, I'm sure, concern, right?

RGK: It does, it does. And you hope, of course . . . I think really the labeling is our primary mechanism to inform people, and certainly to inform people in any kind of detail about the data, because we have press announcements and we have a website and we have these DSCs, these Drug Safety Communications, which are out there on the Web, and we make companies send healthcare practitioners letters. So there are the mechanisms to inform people. But the label is the main thing, and you

really do hope people read it. We can't force people to read it, but . . . And nowadays, of course, patients are more educated. They're on the Web, they have access to the labels, so you count on that, too. But you can't be completely certain that people are reading it and they're practicing medicine in as an informed a way as you would hope.

And I have to say, we talk about that all the time, about how nobody reads the labeling, and I have to tell you, it's somewhat ironic, if that's the right word, because we spend a tremendous amount of time writing labeling, a tremendous amount of time. And many, many, many, many people are involved in it; many, many more people are involved writing labeling than when I got here.

When I got here, we had, the phrase was, "Rally around the Wang." You know, when I got here, there were no computers; nobody had a computer, and we didn't have word processors. Eventually, we got dedicated word processors, which was the Wang; I guess that was the company. And we would rally around the Wang. You know, the team would sit around the Wang; Paul Leber would be at the keyboard, and we'd write labeling. And you'd send it to the company, and you had a back-and-forth, you negotiated, and we were done.

But now there are many, many, many more people. You know, we have so many more consulting groups that are involved in labeling, the advertising people, the maternal health staff, pediatric and maternal health staff, there's the post-marketing people, there are any number of women's health issues, so it's a much huger place than it was when I got here, many, many more people with many different types of expertise, and they are all involved in the patient labeling group. We even have a labeling group. We have this PLR group which deals with the label in toto, writ large. So there are many, many, many, many more groups involved in writing labeling now, and it's much more time-consuming. I think the labels are better than they were, but there are many, many more people involved in the process.

JS: It's a manifestation of a great deal of scientific thought that goes into the label, but I gather there's also an effort that goes into it that looks at it from the perspective of the receiver of the label and what they're looking at, right?

RGK: Yes. Well, the whole PLR, Physicians Labeling Rule, which was instituted a few years ago, which completely changed the structure of the label, that was done, I believe, because people felt, you know, the

structure of the label was entirely driven by a rule, regulations. You know, it's in the Code of Federal Regulations, 21 CFR 201.57, is the labeling regulations, and you go there, and it tells you exactly what the structure of the label must be. It doesn't tell you the specific facts; they vary from drug to drug, of course. But the headings, the sections of the label, are in the regulations, and those regulations have the force of law, so the label has to be in that format. So there were old regulations, and then a few years ago they were changed to this so-called PLR, Physicians Labeling Rule, and that completely changed the structure of the label. Same content, more or less, but it completely revamped the structure. And that was done because I believe we had a lot of evidence that people found our labels very hard to read, hard to find the critical information. And most of this came from physicians. Patients weren't reading labels very much back then.

So the structure of the label is completely different, infinitely improved. It's much easier to find things now in the label that you want to find, like dose, or even indication, what it's indicated for. It's an infinitely better label, including at the very front is a half-page of what's called highlights, and it lists in more or less

bullet forms the really important parts, the really important things you need to know, like what are the big-ticket safety issues, what's the dose, and what's the indication. So, that was put there, as far as I know, because some people don't read the label, and people want to know what really do I have to know about this drug, and they look at the highlights and go, oh, okay, it causes this, or this is the dose in people with renal disease. So the big-ticket items are extracted out in a half page right at the top, and then the details are in the actual label that follows, but even that actual label is infinitely better structured so you can find things that you want much easier. Right now, I go back to an old label, I can't find anything, and I used to write those.

JS: [laughs} That's not a good sign.

RGK: No. So, right. So, where's the indication? I can't find it. I'm flipping pages, you know.

It's still long, it's still long.

So, it's completely different. And that was instituted, presumably, because a lot of people were having problems reading it, so that was a good thing that we did. It's been a lot of work to transition to that, but it's been worth it.

JS: Well, this is fascinating, one of these earliest drugs that you were involved in had such an important role, not only in your own development, but in the way the agency communicates; it was very instructive.

I want to go back to and actually stay in this period a little bit before we move forward in your time in the position, because one of the things I think you got involved in was the IND rewrite. Unless I'm mistaken.

RGK: Well, I wasn't involved in the IND rewrite, in sort of drafting it. I did cause a stir inadvertently as a result of that, but . . .

JS: Well, let me just say this, and I'm interested to hear about this. When you arrived in 1983, the agency, I believe, we weren't in the middle of the NDA rewrite, maybe toward the back end of that, and there certainly was the plan to proceed from that to the IND rewrite. And so I was interested to hear what happened with that, and maybe, if you could, just say a couple words about what these rewrites were about.

RGK: Yes. Certainly, I think the NDA rewrite, and I guess the IND rewrite, really sort of codified our better thinking about what data was necessary, how these things should be structured, because when I got here, there were rules and there was a law that said you had to have this in

your application. But it was generally poorly done. It was difficult to find things in an NDA, and even an IND, and we weren't nearly as smart about it as we became.

So, my recollection is that the NDA rewrite sort of -- and I don't remember it perfectly clearly, was more explicit about what needed to be in there, more data. So, people became aware that there were certain types of data we needed, presentations of the data, statistical analyses. It had to be more sophisticated than it was, because when I got here it wasn't particularly sophisticated.

And the IND rewrite, again, I think it was more explicit about what needed to be in an IND and this sort of thing, and the structure of an IND. I was here when it happened, but I wasn't involved in the genesis of any of that. But I did do something fairly foolish related to it at the time.

My impression of the IND rewrite -- which I think was '87 but I could be wrong, it could have been earlier -- was that it was much improved over what it had been before, what the rules had been before, but that in essence, by that time, it pretty much had codified what we were doing already. So, in other words, we were already asking of sponsors to submit various types of information in certain formats that the IND rewrite codified. So, my perception

of the IND rewrite was that it was a good thing, but it wasn't, in practice, it wasn't anything new. It was definitely new compared to the old rules, but in terms of how we were interacting with companies and what we were asking them for, it just sort of put on paper what was already happening. So that was my view of the IND rewrite, which was a good thing; that was a good thing.

And for some reason that I cannot possibly fathom, at a Food and Drug Law Institute meeting, I was asked, by the people here to give a talk about the IND rewrite. And this was the view I had of the IND rewrite, which to me seemed perfectly reasonable. But, of course, at the time, the agency was touting the IND rewrite as something brand new, as something that would expedite drug development and was really going to just make things qualitatively, exponentially faster, etcetera, which was true compared to the old rules, but it wasn't true compared to what we were actually doing, because these rules just described what we were doing -- at least that was my view.

So I was young and incredibly naïve. But before the talk, my boss, who defended me always in my time here, he told the higher-ups, whoever they were.

TAPE 1, SIDE B

"You know, he's going to say what he thinks." They never asked what I thought. But they said, "Fine, sure. He should say what he thinks," because I did. I said, in a room full of food and drug lawyers and drug-company people, and I was relatively new here -- I didn't give many talks -- and I said, "Look, we have this new IND rewrite. It said this." And I said, "But don't get too excited because it's really, you know, it's just sort of business as usual," which was exactly not the message that the agency was putting out at the time. You know you've done something eye-catching when you hear sort of a murmur through the crowd. So when I finished my talk, I hear this sort of murmuring, and I went, "Oh, I shouldn't have said that."

So as far as I understand, Paul Leber was on the phone for several days, trying to keep my job for me. I believe that upset a number of people in upper management, whoever they were. I barely remember who they were at the time. Because, of course, I was speaking exactly the opposite of what the agency was officially saying. The agency was officially saying this is brand new, it's going to transform drug development, and I was saying it's really business as usual, which it was in my view. But it was

very different from the old way. But I was sort of subverting the agency message.

JS: Well, maybe if they had charged you to give more of a historical talk about it that would have made more sense. It would have comported with your view of it as well.

RGK: Yes, yes, right, right, right. But that's not what I chose.

But anyway, so, I'll be forever grateful to Paul Leber for giving me the job and for ensuring I kept my job.

But it was much better than the old. It allowed us to have more data and it was definitely better than the old way.

JS: It wasn't very long after you arrived here, after 1983, and within about a year you became group leader. As you said before, you were the group. I'm not sure I would say something about that. But you became a Group Leader in neurology, in the Division, and you remained in that. Of course, you were Deputy Director, too, from 1986 until '99 as well. I was curious in your characterizing different responsibilities you have as the Group Leader as opposed to a Medical Officer, but it sounds like, at least early on, there really wasn't much difference in responsibility.

RGK: No, not much, not early on, because I was, there were only two other people but really not terribly functional. And I was the only one trained in neurology in the group, in the neurology group.

JS: Well, what were the others trained in?

RGK: You know, that's a good question. They were here a very long time. It might have been something in general medicine or that kind of thing. But we had a dentist on staff. It was not what you think of nowadays as a well-staffed division. There were three groups in the Division when I got here. There was a neurology group, a psychiatry group, and the drug-abuse staff, which ultimately went to a different division. So we had those three groups.

The drug-abuse staff had some pharmacologists who knew about drugs of abuse. I'm trying to think if when I got here there was a physician on the drug abuse staff. There might have been a physician not particularly trained in drug abuse.

And in the psychiatry group, there were a couple of psychiatrists.

And in the neuro group, there were sort of people who'd been here a very long time, not particularly functional. They weren't trained in neurology. They might

have been trained in internal medicine, probably mostly. But there were only a handful anyway.

So, I did a lot of the primary review work. And these other people did a little bit, so I was sort of the team leader for that. But there wasn't a lot coming out of that other portion.

JS: And I guess it had been a long time since anorectics had been part of this Division as well.

RGK: Yeah. I think, yeah, yeah. It's hard to remember exactly what we had, but we did have the drugs of abuse. We had drugs for nausea and vomiting, which we haven't had in forever, but they were here then.

JS: I assume it wouldn't have fallen under your group. But, of course, by this time, by the time I've talked about here, since you were the Deputy Director of the Division, I assume you would have had an interest in this. The 1980s was an interesting time for work in this Division. There were a couple of products in particular that came along: in '87, Prozac; in '89, Clozaril.

RGK: Yeah, right. But the reality is, I had very little to do with, almost nothing to do with the psychiatric drugs, even though I was Deputy Director. And it's sort of interesting because to me, the psychiatric end of things was more or less a black box. I was, while I was

the Deputy Director, I was also the Team Leader in Neurology, and we ultimately, over time, we developed several teams in Neurology, so as Deputy Director, I really mostly, almost entirely functioned largely as the head of the Neurology Group here. So, I mean, I had very little to do with psychiatry, almost nothing.

JS: And their Group Leader was . . .

RGK: Tom Laughren became their group leader shortly after I came here. He's recently retired too. So he dealt with all the psychiatry drugs. Paul Leber, of course, was Division Director, and he was a trained psychiatrist. He was a pathologist and a psychiatrist, so he took a great interest in the psychiatry end of things. Also the neurology end, but he had a bigger interest in psychiatry, and he dealt with Tom directly. And I really, even though I was Deputy Director, my role was limited to running the neurology side of things. So I actually was not directly involved in Prozac or Clozaril or any of those. I mean, I sort of was peripherally aware of it. Really, there was almost no interaction between the neurology group and the psychiatry group. And as Deputy Director, I really played no role in psychiatry.

My primary role as Deputy Director for most of that time, almost all that time, was to fill in when Paul Leber

was not here. So if Paul would be at a meeting, he'd be away or he's on vacation, which he rarely took, but when he was somewhere else -- and he went to meetings, giving talks, that kind of thing -- I would sit in for him, so I would sign letters for him, or if there was an issue that came up, I would deal with it. But when he was here, which was 99 percent of the time, I really pretty much focused on neurology, even though I was Deputy Director.

I was not the kind of a deputy which is more common now, which is, I mean, there are many ways people use a Deputy Director in Divisions. Some Divisions split the division so the Director deals with some drugs, the Deputy Director deals with other drugs. In some, a Deputy Director is, sort of is an intermediary between all the drugs and the Division Director . . .

When I was Deputy Director, I mostly filled in for Paul when he wasn't here, but 99 percent of my time was spent doing neurology.

JS: Well, then I guess let me ask, when you became Division Director in 1999, did you follow the same model?

RGK: No. When I became Division Director in 1999, I panicked, because I knew I was going to have to take care of psychiatry. I'm sort of following the Paul Leber role; see, he did both. He was the one person who did both. And

so the first thing I did is I went to Tom Laughren, who by that time had been here a long time, as I had, focusing on psychiatry; he knew everything about the psychiatry division. And I said, “We have to split the Division,” I said, “because I don’t know anything about psychiatry.” And now I was Division Director and I was responsible, not just for neurology anymore, but for psychiatry. And he said, “Well, let’s just see how it goes.”

So as Division Director, I was technically head of psychiatry. Tom was head of psychiatry, but I functioned as a Division Director the way Paul did, which is I went to all the psychiatry meetings, I went to all the industry meetings for psychiatry, I became a single division director dealing with both psychiatry and neurology. And, of course, I had much more experience with the neurology side of it, and I had no experience with the psychiatry side of it, but I learned.

As I say, I was quite anxious at the beginning, I didn’t know anything about it, and the reality is these are obviously different fields. In this case they happen to be related fields, but they’re different. But there are many sort of generic skills that you need to acquire to know about developing drugs or regulating the development of drugs that are, in my view, largely generalizable -- not

entirely. Obviously, every field has their own specific issues, but developing drugs, you know, the skills you need about clinical pharmacology or statistics or clinical trial design. The law, the big-ticket items that you need to know about developing drugs for neurology, I found generalized largely to psychiatry, the individual issues in psychiatry, the diseases in psychiatry, the course of the diseases, the patient population, and all of this is specific, and I had a team of psychiatrists who knew all about that, who educated me. And so, over time, I went, as I say, I more or less sort of doubled my workload instantly the day I became Division Director.

But I learned; I think I learned. You'll have to ask others how successfully I learned. But I took over as Division Director of the entire division, and with the help of Tom and his group, I learned, I think, what I needed to know about developing drugs for psychiatry, and we went on like that till they split the division. We were administratively split into separate divisions, I'd say around the time we moved here, maybe eight years ago. So eight years is -- what are we, 2013 -- so 2005 or thereabouts.

JS: So, before that happened, the Division was facing a lot of interesting issues, labeling issues, particularly with the selective serotonin reuptake inhibitors (SSRIs)…

RGK: Suicide.

JS: Yeah, the suicidal ideation and issues like that. And that's just, I mean, to an outsider, is fascinating, but from this end it might have a different perspective. We were balancing so many different kinds of approaches to this from the outside, and even within the agency, there was quite a lot of disagreement. And eventually, I guess it was 2003 or 2004 that we did come out with the black-box warning about this problem with, particularly with children.

RGK: Right. In fact, it seems to go away as people get older.

JS: Can you just briefly narrate how we negotiated this problem from the time it presented itself to us to the time that we actually came out with the label?

RGK: Well, my recollection is that one of the reviewers noted an adverse event in one of the development programs, I believe in the pediatric development program, where a particular behavioral adverse event -- I think it

was noted as emotional lability -- and he wanted some more explanation about what that meant. And so we contacted the company, and my recollection is the suicidal ideation, suicidal behavior adverse event sort of came out of that. When the company responded, it looked like maybe it was, if I recall correctly, sort of suicidality. We decided, well, maybe there's a problem here. And ultimately we decided to do a formal analysis of this drug and suicidal behavior and suicidal thinking or suicidal ideation. So it came out of, if I recall correctly, it came out of that first drug. It was a medical officer who wanted more information on an adverse event that he didn't feel was really described adequately. And, of course, that's sort of a generic problem when sponsors describe things. They may pick a term that is sort of on a list somewhere that's an acceptable term, but it's not really clear what it meant, what these things mean all the time, and you have to do some digging. Of course, sometimes sponsors label things in a certain way to sort of hide a problem, but I don't personally think that happens very often. Sometimes it's just a question of, you have to choose from a list of things what to call a particular event, and you choose something but it's not really right or it's not really clear. And one of our jobs is to ferret out what actually

did happen to the patient, because you can skew things that happen to a patient by what you call them.

When the sponsor submits an NDA, and you get lists of adverse events, you don't get -- well, somewhere deep in the application you get it, but when they present it to you, they combine these things. So, if somebody's lightheaded -- just as a simple example -- or the room is spinning around, the patient may say, "Well, the room is spinning," and so somebody writes that down, a so-called verbatim term. Somebody says, "I'm lightheaded," so somebody writes that down. But then somebody at the company has to put these together and subsume them under another term, because they don't give us tables of adverse events of what we call the verbatim terms, terms that the patient actually used. They classify them. So a company might put together room spinning around and lightheaded, and they may call that dizziness. That's not unreasonable. The problem is, those two things are very different things. Somebody might describe lightheaded and might use dizziness as a synonym for lightheaded, and some people might use dizziness as a synonym for room spinning around, but those are completely different things, and you would obscure that. You wouldn't know what you're talking about if you see the company reports, "Ten percent of patients were

dizzy." What does dizzy mean? Does it mean lightheaded, does it mean the room is spinning around? Does it mean they fainted? What does it mean?

So, things can get lost when they're coded a certain way, when they're given, when adverse events are classified in a certain way. And this started because somebody classified something as emotional lability when in fact, I think, if I'm remembering correctly, it was suicidal ideation. So, from that, we asked for all their data on suicidal thinking and behavior, we asked them to do an analysis now.

I think really the big internal debate about that was, I don't remember the chronology exactly, but it had to do with something like this. When you get reports of something, let's say with one particular drug in a class, like the antidepressants, you ferret out what's going on and it looks like, well, maybe there's a signal of suicidal thinking for one of the antidepressants. You could think about changing the label. If it gets to the point of having to put that in the label, describe something bad in the label, you have to think about, well, what about the other drugs that are approved for that indication? Many of them, of course, as far as we know, work the same way. So, first of all, if you have a group of drugs, like the SSRIs,

they more or less have the same -- they're all a little different, but they primarily, we think, work the same way biochemically, pharmacologically. So if you detected a signal of something with one drug, it's not crazy to think, well, gee, maybe the other drugs have that too. It's just that they haven't looked as closely at their data or they haven't looked at it in the same way that the first company looked at it, or in the way that we asked the first company to look at it. So you have to think about asking all the drugs that have the same indication to do the same sorts of analyses, because if you don't, not only are you sort of, in some sense, unfairly targeting that first drug, but when people read the label for that drug and it says suicidal thinking, it's going to shift them to these other drugs which don't have that in their label, but in reality may have exactly the same risk. So you have to think about asking all the drugs to do the same analyses, and then you have to think about what's the appropriate analysis to do.

JS: You know, we did this in the post-DESI period with anorectics, too. We did a massive study of thousands and thousands of patients over 20, 30 years, just because they all sort of acted much the same way.

RGK: Yeah, well, right, right. So you have to think about that, because if you label one drug, it's unfair

perhaps, but that's less important than the fact that you're going to shift people to these other drugs and they're probably just as risky.

So, these are complicated matters because you have to think about that, and then you have to do these other analyses, and then you have to figure out what analysis is the right thing to do, and these things all take time; they take a lot of time.

So, ultimately, what this came down to was that we thought we should do a meta-analysis of the antidepressants or the SSRIs, looking at suicidal behaviors, actions, suicide, if there were any, and suicidal thinking. And at some point, we decided that it looked like maybe there was a signal, but we weren't ready yet to definitively say there was, and we were going to embark on a systematic meta-analysis. But some people in the agency, on the staff, thought that, at an early stage, we had enough to conclude that the drugs actually did this and that the label should be changed and that sort of thing. Others in the division, including myself, thought we were not there yet and that we had to go through this systematic analysis. And we went to an Advisory Committee before we did this systematic analysis and we said, "Look, here's what we've done so far. It looks like maybe there's something there,

but we don’t think we’re ready to put it in the label yet. We want to do the following analyses,” and the Advisory Committee endorsed that view, that we weren’t yet ready to put it in the labels and that we should go ahead and do the systematic analysis. But there were people on the staff who felt that we were ready to do it at that point, and that it was, look, if you think you’ve already concluded that the drugs cause suicidal ideation and you don’t put it in the label, that’s wrong. But we didn’t think we were, and there was some internal disagreement about that point.

JS: But what about the issues with coding that you brought up?

RGK: Well, what we did is we asked the sponsors, as part of the systematic reanalysis, to go back and to look at all the reports that were potentially relevant, suicide related, and it was very complicated, but we sent them many directives, letters about how to analyze their own data. And we gave them a string of terms that could possibly have captured, we thought, anything that could possibly have been suicide, and they had to capture those patients who had any of those terms, and then they had to write up what we call narratives, you know, texts, descriptions of what happened to those patients, what the events really were. They had to go back to their records, and they had to do

this without mentioning which treatment they were on, and then they had to give these narratives to a third party who was blinded, didn't know the treatment assignment, and had to decide, according to some classification of behaviors, was it a suicide attempt, was it suicidal thinking, was it self-injurious behavior that had no intent. You know, there's this phenomenon amongst adolescents of cutting themselves. Most people don't think that's a suicidal behavior even though they cut themselves with a blade and it's sort of an anxiety-relieving thing. It's self-injury, but it's not with intent to kill themselves.

So, all of these events had to be classified into one of these classifications that were on a scale that was created by Columbia University, so it was a very complex thing. And we asked for all this data, and we did our own meta-analyses of all the trials, because any given drug-development program was unlikely to have enough of these events so that you could say something about whether the drugs caused it or not. So, in a case like that, it's common to put all the data together, assuming all the studies were combinable. You know, it's a complicated statistical question as well. And we combined all the data from, I forget how many studies, and we believe a signal emerged that there was a risk of increased suicidal

behavior and suicidal ideation in these drugs, with these drugs, and it was true, by the time the Division split, we knew it was true or had concluded it was true in younger kids. As it turns out, after the Division was split and I was no longer involved in that, I think they did subsequent analyses, and it turns out it was true up through, I guess, young adults or something. So it really seemed to be age related.

Now, why these drugs did this, I don't think anybody knew or knows. They were effective antidepressants, and if you're depressed, you are what's called motorically retarded. In other words, when you're very depressed, you can't do anything; you're too immobilized psychically. And as you come out of the depression, you're more animated; you begin to be more functional. And some people think that the reason we were detecting this increased incidence of suicidal thinking, let's say, was because the drugs were working, they were making people less depressed, and now they were able to talk about what they were feeling. So it's not like it actually made them more suicidal; it just made them more likely to report this. Now, I don't think anybody really knows.

JS: Overall, aside from the side effects, were the drugs functioning to keep people from killing themselves?

RGK: Well, that's a good question. I think the data is still out on whether or not these drugs overall decrease suicide. That's something you can ask people in the psych group. But I think the jury's out on that. They're definitely effective as antidepressants, make them less depressed.

And there was some question -- I have to go back and think -- shortly afterwards, there was an increase in suicide, I think, that was reported. And people were saying, "Well, look, now that you changed the label and you put a boxed warning, you're scaring people away from using these drugs." But that was, I think, a little blip, and it came back down. So I don't think people think that people who need it aren't getting these drugs. For one thing, all the drugs have this in their label; they're all the same. So it's not like you can say, "Well, I'm not going to use this one, I'm going to use that one." And I think people think you have to treat depression. So you have to treat it. I think most of us here think that that label isn't discouraging people from using them.

Now, of course, these drugs are used a lot off-label too, and maybe some of the off-label use went down. But when you have a serious disease, most people think you need to treat it, so the label informs people. It doesn't

necessarily, it doesn’t prevent them from using the drugs. Of course, if you’re on the drug and you become suicidal, you might decide, well, maybe this is the drug. But I’m not sure it *a priori* scares people away from using them.

You know, we had an advisory committee, at least one, and it was incredibly intense. We had people in the audience, this was a public session, and people accused the FDA of killing their daughter or their son who committed suicide while on these drugs. But, of course, people with depression commit suicide. And one woman basically accused Tom Laughren at the meeting -- this is in front of hundreds of people of killing her daughter, and it was horrifying.

So, needless to say, it was an incredibly emotionally charged thing, and then there were people on staff who felt that their opinions weren’t being heard because they thought the drugs should be labeled sooner than we thought. So it was a mildly unpleasant time. But I think we did the right thing.

JS: I didn’t realize this until looking at a few things before I came to talk with you -- that here we are in one Division, your Division, and this might be a reflection of how expensive the products are, but there are two classes of drugs, the antidepressants and the antipsychotics, that are among the four top-selling classes

of drugs there are, and these are both drugs that were under the Division, one Division at the time. I can only imagine this must have added to the level of stress, among other things, because it's a huge responsibility. This is obviously an extremely busy Division, dealing with so many products that are coming in and of such a concern as what you just narrated.

RGK: Yeah. Well, you mean just in general, a stress, or the . . . You mean just in terms of the ubiquity of the drugs out there?

JS: Yes, absolutely.

RGK: Well, you know, it's interesting. There's stress and there's stress. Again, I can only speak personally about stress, and there's plenty of it here. But it's emotionally difficult to hear somebody accuse you of killing their child because you let these drugs out there. But you understand that that's probably the worst possible thing that could happen to somebody, is that their child died under any circumstance, let alone commit suicide, and you understand that people have to blame somebody for that. And, of course, you think about whether you're to blame for that. I mean, everybody's different, you know. I'm sure there are many people who think it's ridiculous. The drug didn't do it and it's not my fault.

But I think people do think, well, maybe, yeah, maybe we made the wrong decision; maybe we should have removed these drugs from the market. But I don't think anybody who's looked at the problem, you know, I'll say objectively, none of us are objective, but who doesn't have sort of a personal connection to it, think that, let's say, in that case, that we did the right thing, that we labeled them when we had the evidence that they should be labeled, and we keep them on the market because they are critically important treatments for a horrible disease, and that's true for most of the diseases we deal with, I think. But nobody likes to hear that. Nobody likes to be blamed for it. And it's useful, I think, to think about these things.

And you read all kinds of things about the FDA, blame us for everything, approving a drug, not approving a drug, so it's worth sort of taking stock and, unless somebody is just completely out of their minds and irrational, it's worth listening to these people. So you rethink things. But I think mostly we make the right decisions.

So there's that stress when there's sort of a personal attack. Let's put it that way. I don't know if that's stress, but it is painful to hear.

The fact that the drugs that we approve and regulate affect millions of people, I personally, I don't see that

as the stressful part of the job. I think you're always aware of it. And, again, maybe everybody else feels differently, feels that it's stressful. We try to do the best job we can do, and it can be stressful doing that for a lot of reasons, because it's sometimes very complicated and you don't know what to think, and there are always time pressures, and that's extremely stressful, at least to me personally. And there are always people asking you to do 50 different things around here, and that's stressful. But the fact that there are many people out there whose lives will be affected by what we do, whether you turn a drug down or approve a drug, I don't find that aspect, which of course is a huge aspect, I don't find that aspect of it stressful, particularly stressful. I don't think, oh, my God, millions of people are going to be taking this drug. I'd better get it right. I just think I'd better get it right. I know what the stakes are. And, again, this is a highly personal reaction. I don't find that part of it stressful. I find getting the job done and getting it done well, because I think we should do the job well, stressful.

Just like I don't worry about the press. I don't find, I mean, you might find talking to the press stressful because they're trying to catch you on something or they're trying to make a controversy where there is none, that kind

of thing. But if the press writes “bad FDA” or Congress, I never think about, oh, Congress is watching or the press is watching. Again, I’m speaking entirely personally. That never enters my thinking. I mean, we talk about it, but it’s never an important, it’s not in the back of my mind like, oh, I’d better do this because Congress is watching me. We just try to do the best job we can do. And you know Congress may ask you in or the press may call you, but it’s not a factor. And, similarly, the fact that these things affect millions of people’s lives explicitly is not, in my case, doesn’t contribute to the stress. I just have a job to do.

I know what the ramifications are, but I’m just trying to do a good job. I’m trying to get the right answer, and that can be hard scientifically; it can be complicated. Thinking your way through a problem and getting to the answer that you think is right, that’s hard. It can be hard; it’s not always hard, but it can be hard, and that’s stressful, trying to figure out, what should I do. But I figure if I stress over that, I don’t have to stress over millions of people take these drugs because that’s my job, trying to get the right answer.

I don’t know if I’m sort of articulating this adequately, but I know millions of people take these drugs,

and it’s one of the things I think is great about the job, by the way, because it is a job that has practical importance. I can’t think of too many other places where you are intellectually stimulated to the degree you are here, and what you do has an important effect on people.

JS: That’s the nature of public health, I suppose, isn’t it.

RGK: Sure, absolutely, absolutely. And I often think about the academic life. I mean, I’ve never been an academic, but it’s an attractive lifestyle. But you think -- and this is unfair to academics, I know, but it’s an intellectually stimulating environment, but the part about millions of people being affected by what you do, that’s probably typically not the case, whereas here, everything we do affects lots and lots of people in a very fundamental way. But I don’t think about that so much. Of course you know that’s true; that’s why we’re doing the job. But that end part of it, that doesn’t give me stress so much. I just figure if we do a good job, that’ll be a good thing.

JS: One of the things I can imagine, as you said, in trying to do the right thing, do a good job, is perhaps come up with a management style that helps you do that. And I know yours has been, as you said in other places, that what you try to do is bring in as many perspectives as

possible and give everybody a chance to voice their opinion about a subject. It might be an easy one, might be kind of a nasty one, but then come to a decision based on that. And I'm curious. How does one do that, particularly in cases where you have pretty strong disagreement? I'm sure that happens.

RGK: Yeah, it does happen. I'm quite certain I don't always do it successfully, but I think you just have to constantly remind yourself that everybody has something to contribute. Not only do they want to contribute -- by the way, not everybody does want to contribute; many people are willing to just sit there quietly -- but most people want to be heard. So I think you need to always remind yourself, because sometimes there are, obviously, 60 people in a Division and there are 60 personalities, and some are forceful and some are quiet. So you do have to -- I say this as if I do it routinely; I try to do it, but I'm not always successful. But you sort of, I think that you kind of have to get the message out that everybody's got to have a chance. See, I think you should try to create that culture and you just . . .

Most of what I do is go to meetings, so most of this stuff happens at meetings, because everybody has a written, like if you have an NDA, everybody has a review, they get

to write what they want to write. They give their opinion in their reviews. They have to do that. It's expected. Every reviewer has to contribute a review. But in a meeting, that's where personality can get in the way, because somebody is loud or interrupts and somebody else wants to say something and they don't get a chance, because when you're interacting with people, that's when all of the dynamics occur. So, I don't know; I just try to be aware of it. And we do have people who interrupt; we do have people who are loud; we do have people who like to control the message, and I just try to make sure that everybody who wants to say something gets a chance to say it. And I'll interrupt. I mean, I'll interrupt somebody who's interrupting. So I just try to give everybody a chance. And I'm sure I don't do it successfully all the time; I know I don't. But I try to be aware of that.

And the other thing, besides just giving people a chance to speak, is you want to hear what they have to say, because you do want to make the best decision you can make. And one thing I've learned, if I've learned anything here, is that you don't have all the answers, nobody does. So you can't do the job without hearing what other people say. It doesn't mean you have to agree with them. They may say something ridiculous and you're going to dismiss it, but

you still have to treat them well. You can't dismiss anybody in public. But you want to make the best decision you can make, so you've got to hear what people say. People might have thought about something you didn't think about.

And sometimes it's hard. I don't know what to think. In fact, most of the time I'm in a meeting, you can always tell -- I don't know; I assume people have picked this up -- but if I'm in a meeting -- and I more or less call all the meetings -- and so we get to the point where all the issues have been discussed, and now what's left is a decision, because that's the hard part, and you can always tell I have no idea what to do when I ask, which I do often, "All right, what do people think?" because that means I don't know what to think. I mean, I have an idea of what to think. Because sometimes it's sort of obvious and I'll say, "All right, look, it seems like we should do this," and everybody agrees. Most of the decisions are made, there's a consensus in most things. But when I ask the group, which I do frequently, "All right, what do people think?" I don't know how they interpret that, but that's coming from a place where I don't really know what to think, and that happens a lot. And the only way you sort of figure it out is everybody says what they think and

why they think it, and you ask them, “Well, what about this?” So you come to a reasonable decision, I hope. Most of the decisions are reasonable. They’re arguable. There’s no right answer to 99 percent of what we do, but you just have got to hear people out.

I mean, that’s one thing I learned here, is there are at least two sides to every story. There are probably 10 sides to every story, and you’ve got to hear it because you really want to make the right decision. You could be completely forgetting something, and if you haven’t asked people, you’re not going to know.

Now, I’m the biggest interrupter. Somebody came up to me once after having been in a meeting. I was Division Director, and this person came to the Division not that long before they came to this meeting, and this is a person from the Midwest, I learned. And she came up to me after the meeting and she said, “I don’t think I can work with you and your New York style.” I didn’t know I had any style, quite frankly. But I knew what she meant. I mean, I interrupt, I’m impatient, I speak quickly, I’m loud. I didn’t know these things till I got here, by the way, because everybody was like me that I knew. And we got an hour. Most meetings are an hour, typically. We’ve got to make a decision. Are we going to let this study proceed,

or are we going to do this or that, change the label, whatever? Most of the decisions, they're important decisions.

JS: But the time limit is a good idea.

RGK: Well, you have to, because I have nine meetings a day. They can't be more than an hour. So the clock's ticking. And if somebody speaks slowly, boy, talk about stress.

JS: That's Omaha.

RGK: Yeah, right. Talk about stress. That's the biggest stressor for me, is, you've got an hour, everybody says their piece, but if they speak slowly, it's really hard. And most people do, by the way. Compared to me, they do.

JS: From your perspective, I'm sure that's the case.

RGK: So, I love these people, and they're incredibly smart, incredibly hard-working, but I have not successfully gotten to the point where I've gotten them to speak fast. But some do.

So we've got to make a decision. I've got 10 minutes left, and I've got to get there. So I'll interrupt because I'm trying to get to the point. So I know I do that. But I do try to let people have their say. It's important to them and, just on a practical level, it's important for me

because I've got to hear what people think because I don't know. I've been around a long time and I know how to think through most of these problems, but a lot of them are on the borderline and you really want to hear . . . People disagree and you've just got to, when people disagree, you've got to acknowledge their point of view, but you've got to make a decision. So I don't mind disagreeing with somebody as long as it's respectful. I always say, "Look, I understand your point, but I really think this." And I think people, if you treat people with respect, they want to be heard, they're heard, that's what most people want.

That's the other thing I learned here, is that there are great people from all over the world, let alone the country. I'm from New York. I didn't even know where Kansas was. I know where it is now because I have a good friend who lives there and who work here, moved to Kansas. I've been there.

JS: One of the three.

So, in the area of decision-making, I also wanted to ask a little bit about what role -- you've found in your own experience -- what role your Advisory Committees have had in helping or hindering your decision-making here in this Division over the 30 years you've been here.

RGK: I would say, as a general matter, they play an important role, but as a general matter, their recommendations have been pretty predictable. We go to the Advisory Committee for a few restricted reasons, because it's a lot of work; it's a lot of work to prepare for it, and it's a lot of work for the advisors because we send them reams of data to review. We send them packages of data to review; the company sends them packages of data to review; we don't give them a lot of time to read this stuff, so it's a lot of work for everybody.

So, we go when we really don't know what to do, or we go because it's sort of a politically sensitive issue and you want a public airing of it. We don't go routinely; there's no point in going routinely. We know what they're going to say, and it's a lot of work, and there's no point in it. I think it's almost abusive to our staff and to them to go on sort of routine stuff.

JS: So, what would take us to an Advisory Committee meeting?

RGK: Well, like the suicidality analyses, which were very controversial on suicide and psychiatric drugs. And, by the way, we did the same analyses for anticonvulsant drugs, too, later on, these meta-analyses for suicide, and that was controversial too. So something like that. Or

this drug I was talking about earlier, should we continue this drug, should we not. We might be contemplating taking the drug off the market because of some toxicity and we want to know what outside experts think because taking a drug off the market is a big deal again, for us, because most of the diseases we're treating are bad diseases. And even though they may have 10 treatments, it's still not enough. So, if you're going to take a drug off the market that's useful, you want the outside community to weigh in on that if you can, if you have the time to do it and that kind of thing.

And new chemical entities we take if they, maybe it's the first time we're ever about to approve a drug for a new indication, and we don't always even go for that; but if the data are questionable, if we're not really sure, there may be some side effect and the efficacy data are not terribly robust. So those are the kind of things we go for.

We just took one in May for a new sleeping pill, a new mechanism, so people are excited about that because it's not the same old kind of sleeping pill; it's a new sleeping pill. But it had some problems. It had some effects on the next day functioning, specifically about driving behavior the next day. People who took certain doses were

impaired in driving the next day, which is a big public health issue. A lot of people take sleeping pills, and if they're impaired when they're driving to work the next morning, that's not a good thing.

So, the company wanted to approve a certain dose, and we thought a considerably lower dose should be approved because it had fewer of those next-day side effects. But the company never, they did one study with that lower dose, and we thought it showed that that lower dose also worked, but the company didn't produce it, they didn't mass-produce it, because they wanted the higher dose approved, so they didn't have that lower dose available to be marketed.

So we went to the committee and said, in effect, look, do you think we should approve it at this higher dose given that the lower dose works, and we sort of got a mixed message from the committee, actually. So, that kind of thing. We say, look, yeah, the drug works, but we think a lower dose should be available, but the company doesn't have the lower dose, they only have this higher dose, and they want to get approval of that one. Right? So, that kind of thing.

So you never know what the issues are going to be. It's always a little twist on something.

But mostly when there is, when we're either about to take an action that we think is going to be controversial, or the drug is sort of politically controversial, which in neurology is not too common, or there's some side effect that we're nervous about approving it with.

JS: How often do you meet?

RGK: A couple times a year maybe, a few times a year in neurology, three, I don't know.

JS: And what's the name of the committee?

RGK: Our committee is the Peripheral and Central Nervous System Drugs Advisory Committee, PCNS Advisory Committee.

We took an ALS drug. You know, ALS, Lou Gehrig's disease, is horrible. There's no potent treatment for it. There was a drug that they had done two studies. One study was positive and one study was very borderline, very borderline results. And there were, I think, like 75 people in the public session speaking, which is an extraordinary number. Normally there's 10. And it was heartbreaking, you know. People in wheelchairs, family members of people who had passed away with ALS -- all of them wanted the drug approved. There's nothing available. It's a deadly disease, horrible. But the data were weak, and we wanted to turn it down, but we wanted public

discussion of it because ALS, there's nothing. You know, it's horrible. Some people's view is, well, anything is better than nothing.

So we took it to the committee and the committee said we should reject it. So it's helpful to have a group of experts publicly say you shouldn't approve this, because then when you don't approve it, it's easier. You're better armed, if you will. And we were picketed outside by the ALS community.

JS: Here at White Oak?

RGK: At Woodmont, when we were there.

JS: So, what was the product?

RGK: It was called myotrophin.

JS: This was around when?

RGK: Well, we were there, so it's at least eight years ago.

JS: 2000, 2005.

RGK: Yeah. Well, probably. I'm terrible at dates. You can look it up. [The protest in Rockville, Maryland, took place in 1997.]

And they actually subsequently did more studies, and those were negative studies, so I think it was the right thing to do. But when you want somebody to hold your hand . . .

So, that's why we go, but we don't go routinely. And most of the time, even when we go, we're pretty sure what they're going to say.

JS: Let me ask, in the time you've been here, how often has the agency and your Advisory Committee disagreed on a decision?

RGK: Very few. It has happened.

JS: It has happened.

RGK: It has happened. In fact, in this last case, this sleeping pill, as I say, the committee gave us a mixed message, one message of which was, approve it, in effect. They said those higher doses that we didn't like, they said those were acceptable doses to approve. Again, they gave us a mixed message, so it was a little ambiguous, but they were very clear on that point. But we disagreed with that. We thought they didn't really consider everything that we had explained to them, and we disagreed.

Similarly, a while back we went for a drug for a disease, a very rare genetic neuropathy, a disease of peripheral nerves. It's a horrible disease, nothing available to treat it. And the committee there said we should approve it based on a surrogate marker, this accelerated approval regulations, which is basically a lab test, not something that's clinically detectable by the

patient. And they recommended we should approve it; in effect, they recommended that, and we disagreed, and that was controversial.

But the vast, vast majority of the time, I would say we end up agreeing. And, as I say, the vast amount of time, it's predictable. We pretty much know what they're going to say.

But I'll tell you, being on an Advisory Committee -- I've never been on one, but it takes some courage because you're out there in public and you have to say your opinion. You know, what I do, it doesn't take that much courage. You know what I mean? Because people know me in the field. But, I mean, I sit in my office -- mostly I'm in a conference room, actually, in meetings. But we make decisions. You know, in some sense we're anonymous. Of course we're not anonymous. Things go up on the Web, everybody knows who we are. We turn a drug down, everybody knows it, and they express their displeasure, or we approve a drug that people think is dangerous, they know who to complain to. So we're not really anonymous. But we do our jobs here in this building, behind closed doors. An Advisory Committee member is sitting out there in front of the public and has to publicly vote on whether they think the drug should be approved or not.

At this Advisory Committee meeting on ALS, this myotrophin, where there were 75 people who made public statements, and everyone was more heartbreaking than the last, people on the Advisory Committee are crying, I'm crying, it was horrible, but the committee voted to recommend not approving it. That took guts; that was courageous, much more courageous than our actually turning it down. So I think that's a big deal, yeah.

JS: Well, they're an important part of our evaluation process.

RGK: Well, yeah. Again, as I say, I think we mostly know what they're going to say, and we mostly agree with them. But there are times where they surprise you and, as I say, they're always helpful, because, as I say, we don't just take the routine stuff. So we go, there's a reason to go, even if the reason to go is we want someone to hold our hands, in effect. We want someone to back us up. That's useful; that's very useful. As I say, there are times where it takes a good deal of courage to deal with.

JS: I'm going to wrap this up pretty soon. A couple questions I had wanted to ask you, though.

One is, your long-term sense, whatever you feel comfortable talking about, the relationship between your

Division, I guess, within the Office of New Drugs and the Drug Safety folks and how that has evolved over time.

RGK: Right. Drug safety, meaning like the post-marketing people? Because, again, there's a lot of drug-safety people now.

JS: Right.

RGK: Well, I like to think that our relationship with the, I'll call them the post-marketing, you know, the OSE, the Office of Surveillance and Epidemiology, those folks. And, again, there's many branches. There's the epidemiologists, there's the people who look at post-marketing reports of adverse events, so there's a lot of groups. But I would say -- and, again, this is my view; you'd have to ask them -- but I think we have a very good relationship, and it wasn't always great. But I have always considered it a very important part of what we do. So we meet with them every month to go over all the projects that we have pending. We have many, many, many projects in conjunction with them.

JS: Projects, meaning . . .

RGK: Meaning drugs we're following that have a post-marketing signal for some adverse event, because our drugs are dangerous, and they're always causing something. So we work very closely with them on those things. And I think

we were sort of meeting with that group on a regular basis. I'll say this. Somebody could contradict me. But I think we started meeting with them well before most other divisions started to meet with them. Now I think all the divisions meet formally. But we were sort of, I won't say the forefront, whatever. We were early supporters of that group.

JS: Since the time you . . .

RGK: Well, since the time I've been here, yeah. Not so much before that, but, I mean, since the time I've been Division Director. I really think that is critical, you know. I mean, we put these drugs out there. We don't know too much about them. We know a lot about them, but we don't know everything about them, and there's always the possibility that something very bad is going to happen, and you want all the help you can get from those people. That's what they do for a living. They're watching what's happening. So I think we get along with them very well. We work with them all the time. We constantly have projects that we're working on together, and they're very good.

And we work all the time with these drug medication-error people. You know those people. We've turned drugs down because we think there's a high risk of drug-

medication errors. The head of that group once, I was going to turn a drug down. The only reason I was going to turn it down was because the drug-error people had determined that there was a risk of medication errors. You know, they go through a long assessment of whether or not they think there might be medication errors because of confusion, name confusion with other drugs or whatever. And they had concluded that there's likely to be medication errors. And everything else was fine. So I was going to turn it down for that reason, because there were things the company could have done to prevent those errors.

JS: Well, this is more than a name you're talking about, changing the name of a drug.

RGK: No, no. It wasn't name, as I recall, it wasn't just the name. Right, it wasn't the name. But, whatever, it was something that led our people to believe that there was going to be medication errors, and I was going to turn it down because of that. I mean, that seemed a perfectly reasonable thing for me, because we thought they could fix it before it was marketed. It's ridiculous to put something out there that you know is going to cause errors.

So the head of that group came to me -- and, you know, we worked very closely together, and she said, "Are you sure you want to do that?" And this is their area. And I

said, “Yeah, I want to do it, sure. It’s dangerous.” And she said, “People don’t do that. People don’t use that as a reason to turn a drug down.” She was all nervous that her group was providing the only basis for a turndown, and I think she was a little nervous for me that I’d get in trouble somehow for turning the drug down for that reason. It wasn’t like the drug didn’t work or it wasn’t like the drug wasn’t safe. It was that there was the potential for a medication error. And I said, “Don’t worry, this is as good a reason to keep a drug off the market until it’s fixed as anything.”

But I tell you the story because I guess it doesn’t happen very often that people worry about that, but I worry about that a great deal. And we worked close enough, we liked each other enough so that she was worried for me that I’d get in trouble somehow for doing that. So we worked closely with them. We sort of, we care what the other one has to say. I think we worked very closely with them.

We’re one of the two divisions, until recently the only division, that has a stand-alone safety group in our division. It’s not neurologists; it’s a group of internists basically whose sole function in the division is to look at safety problems, pre-marketing and post-marketing. And we were the only division, when we were a

combined division in neuropsych, we were the only division that had that. My previous boss, Paul Leber, he started that when he was here; he created that group. And, of course, we kept going, and we're the only division. When psychiatry split from us, they got their own group, because they have the same history as we do of having it.

JS: What about the other divisions?

RGK: Well, the other divisions don't have it. But now every division subsequently, a few years ago, was required to have a Deputy Director for Safety, and they have a Project Manager for Safety, but they don't have a separate group of safety reviewers, or at least they didn't, and we do. And so, I mean, there was some friction there because we had our own safety group. And, of course, there's the other, the safety group you asked about. And the question is, well, who's doing what, what's the jurisdiction, it's the post-marketing thing, do we let our group do it, do we let them do it? So there were some issues to work out, but I think that's worked out very well, I think. And so our safety group works very closely with those safety people, and there's a lot of . . . I'm sure in any organization, there's a lot of sort of jurisdictional stuff, ownership of whatever. But my view

is, anybody who's smart and thought about the problem, they should be involved. It's not a game, you know.

JS: There's nothing inherently more unsafe about the products you're regulating than the products other divisions are regulating, are there?

RGK: I haven't the slightest idea. I mean, what happens outside these four walls, I don't know. Probably. Obviously, cancer drugs are pretty toxic, but they tolerate everything pretty much. Well, I don't know. Our drugs seem to be dangerous. I mean, they're potent and they have problems. For all I know, other drugs have just as many problems. I really don't know. I know we're busy with post-marketing problems all the time.

And as I said before, we tolerate a lot of problems because we think our diseases are bad, and we don't have cures, so we think the more options we have out there, the better. And, as you say, the risk-benefit consideration; when it's a bad disease, you tolerate more risk. So, we don't take many drugs off the market. We have, of course, but very rarely. We approve drugs that have toxicities because we think we can inform people about them, and we may even have the regs that might be able to prevent them, if we're lucky, or minimize them. But we put them out there because they have diseases. And you can count on one

hand the number of drugs we haven't let out there because of a safety problem. It's very unusual. We definitely do it, but it's very unusual. We have a pretty high tolerance.

JS: And in large part because of the power of the label.

RGK: Yeah, because we can inform people. We don't make anybody take the drug, but we give them what we think is the information they need to be able to decide whether they want to treat somebody.

JS: You've been here 30 years. So, looking over those three decades, what do you think have been some of the biggest changes, not only your division -- and you've been in the same division the whole time . . .

RGK: Yeah.

JS: But in the agency overall?

RGK: Well, I would say there have been a lot of big changes. As I say, when I first got here, it was, I won't say it was a nonfunctional division, but there weren't many people with a lot of expertise or energy. So the division -- and this I assume is true for all divisions -- much better people than there were 30 years ago. Again, things got better. Things didn't just get better two weeks ago, I mean, they got better a long time ago, but much more

scientific sophistication in terms of how to review, what sort of data we want from companies, and how we review things. We're just much, much smarter about the work. We've learned as an institution. I mean, the field of drug development has really just exploded in terms of clinical trial methodology, in terms of statistical sophistication and technology.

When I came here, there were no computers. Right? And eventually we got the Wangs, got the word processors; then we got the computers. And the people learned how to use them. And reviewers now, in the review divisions, they don't do the sophisticated statistical analyses, but they manipulate data. We have this staff college where there's formal training in all of these areas. So I think regulatory science, if that's what you want to call it, has progressed just like the basic sciences have progressed in the field.

And that's another thing, of course, the basic science from which all of this springs. I mean, the drugs, obviously we're light years beyond where we were in 1983. We're still light years away from actually understanding what's going on, but there have been incredible advances in -- I speak about neurology -- incredible advances in understanding the brain. Although we're still, in my

opinion, very far away from actually understanding it, we know a heck of a lot more than we knew then.

So the drugs, we have different drugs. Now we're moving into a whole phase of drug development in neurology where we're looking at drugs that people believe affect the underlying disease, can slow the disease process. Well, that never happened before. In the first 15, 20 years I was here, it was symptomatic treatments, which were fine, they helped people. But now, in the world of degenerative disease at least, people think they know enough to be able to design drugs that will slow the disease itself.

Now, nothing's ever been shown to do that in any field in neurology, but we know enough about the science now to be able to design drugs that might do that. And so you have to come up with trial designs and statistical techniques that will allow you to show that, you know, an effect on modifying the disease or slowing the disease. The trials you would need to do to show that may be different from the trials that you need to show some sort of an acute symptomatic event. So, everything moves together, so we're much more sophisticated about how we look at data, about knowing what kind of data we want to have.

The Prescription Drug User Fee Act (PDUFA) laws have been extraordinarily useful, I think. You know, in some sense it's a double-edged sword, but not really.

I mean, I remember the days when I came here, you put an NDA in the trunk of your car and you took it home, and when you got to it, you worked on it. Things are not like that anymore. Now there are deadlines, and they come with their own stress, but things are getting done, you know. There's no drug lag anymore. There may be drug lag in the other direction.

JS: The staff has increased, though, in part because of that, right?

RGK: Oh, yeah. That's what PDUFA was for, was it was intended to increase the staff so that we could do things in a timely way, as a quid pro quo. And a lot of people chafed at the idea because it was, oh, you know, we're the regulators, they're the regulated industry, and now they're paying our salaries. So that is an inherent conflict on paper. Right? We're the cops, we're keeping an eye on them, and they're paying our salaries. Well, it's obvious for someone on the outside to say, "Well, look, they're going to approve every drug now because they're in the pocket of industry." Well, of course it's nothing like that. I mean, they are paying our salaries, but no one is

going to approve a drug because PDUFA fees are here and part of our salaries are paid by drug companies. It just doesn't happen; whereas to an outsider, and even to some insiders when it was instituted, there was protest internally about that for that reason. But in practice, that's just a ridiculous idea; it just doesn't work. That doesn't happen. As I say, nobody approves a drug because there are PDUFA fees. It doesn't happen.

So, but it got us to do things on time. It's still a crunch in many cases. But you have to get the job done. You don't have to come to a particular decision. That's the great thing about this place, one of the great things, is that, yeah, you've got to get it done by a certain time, but nobody tells you, "Look, you have to approve this drug," or "You have to turn this drug down." You've got to do what you think is the right thing to do. You get paid either way. To me, that's the best part of the job, is there's no official bias. We're all human beings, we're all flawed, we're all biased in one way or another, but I get paid whether I turn a drug down or I approve it, so that kind of freedom, that intellectual freedom is huge.

JS: So the user fees have had a huge impact over the course of . . .

RGK: Oh, yeah. And, of course, as they're reauthorized, we get more authorities, but there's more extracted from us, and when we get new authorities, we get new bureaucracy implemented because everybody wants to make sure we're employing, every division is employing the law the same way, which we understand. Of course the institution has an interest in knowing that I'm not interpreting the law one way and this person's interpreting the law another way. It has to be interpreted the same way. So, of course, in general that introduces a new level of bureaucracy of oversight to make sure we're doing things the right way, and of course that slows things down and that increases the burden on the review division because they have a timeline, yet things have to pass through this many layers now before you can act. So, in some sense it's a double-edged sword. I mean, on paper, new authorities are good, but then actually using them requires some more bureaucracy, which makes it more burdensome. So, whatever; we'll see how that turns out.

The truth is, we're all adults, but most of us are children, so you do things because they have to get done by a certain time. It would be nice if we were all self-motivated and we would review every drug in 10 months. But I was here before there were deadlines, and it didn't

happen. So, those deadlines are important, and they work. And, as I say, we're smarter, so we can do more in a reasonable period of time. We can think about data better. So it's hugely different from when I got here, infinitely better. But it is also a more difficult place to work because of all the bureaucracy.

JS: How much bigger is the division -- now? I guess I would have to say both divisions because both divisions were together at the time you arrived?

RGK: Yeah, right. In fact, I was the Division Director of the combined division from 1999 to whenever we split, 2005, whenever it was, and I look at how big the two divisions are now, and I can't believe it. We're twice as big now as that one division was. I mean, I have 60-some-odd people in my division, my division alone, Neurology.

JS: In Neurology.

RGK: And Psychiatry has, I don't know how many. I don't know if it's as big, but it's close. And how many were we when we were together? Fifty total together? I don't know what the numbers were, but we weren't 120. And we had all of that work. Well, we probably each now have more work than we did when we were together, but we were still plenty busy.

JS: On the other hand, the armamentarium for this field has grown incredibly over that time period, too.

RGK: Well, it has. I mean, we're very productive. Again, it's, in my view, everything flows from what comes to us. We don't get to control the input, and sometimes it's very, very busy. And how many drugs we approve is, of course, a reflection of how many we get, so people are churning out drugs.

Now, people say, central nervous system companies, are not as active as they were, because there are a lot of failures. A lot of drugs don't make it through, either because they're too toxic, which is not that common, or they turn out not to work. And these are big, unsolved problems. I mean, why do so many drugs get to the end of development, and only then do we figure out they don't work? So there's many unsolved problems.

JS: Well, you were mentioning earlier the importance of design, the trial design and so on. Are there things the agency can do to contribute to this, to make the system a little more efficient?

RGK: Well, I don't know about efficient, but the question, for example, of trial design, what's the right design for the right outcome for the right disease, we're constantly involved in that. We have pharmacometricians.

These are people who model disease, the course of a disease and blood levels, and come up with designs for diseases that would be capable of showing an effect on disease modification, for example. We've done it for Parkinson's, we've done it for Alzheimer's disease. And these are designs that people then go out and use. They don't always do it, but it has been done. We're constantly interacting with companies about the use of surrogate markers and where they fit in in the design of trials.

So the agency is, I would say, on the forefront of design, clinical trial design issues. I mean, we're always interacting with industry, in effect partnering to come up with a better way forward. You know, they come up with a design, and we're constantly interacting about that design. But in some cases we actually help create the designs in the first place with these modeling efforts and that kind of thing. So I don't know if it makes drug development more efficient, but it does hopefully help move the field forward in creating the designs that people are going to use to determine these things.

We're always talking to companies about early phase studies to try to figure out what's the best dose to use for a definitive trial. Every aspect of drug development we're involved in, and so in that sense you could argue

that could increase efficiency. If you help a company decide very early on what's the best dose to use, you're more likely to have a successful trial at the end, whereas if they do a lousy job finding something out about dose early and they take a dose into a big phase trial that's inadequate, is negative, that doesn't help anybody, and then you've got to go back to the drawing board, or you drop the drug entirely, which may not be a good idea.

So we're involved in every aspect of drug development with companies, and you hope that makes it more efficient.

JS: People talk about the crisis of Alzheimer's coming up in the coming decades. Therapeutically, where do things stand? What does the future look like?

RGK: Well, this is the 64-thousand-dollar question, I mean, or 64-billion-dollar question. Alzheimer's is one of the areas where we're now in a phase where people believe that they have identified treatments that could slow the disease, not just treat the symptoms but actually slow the disease process. Most of the treatments are directed at this abnormal protein that's in the brains of Alzheimer's patients, called beta amyloid, and many people in the field think that beta amyloid is actually what's causing this, sort of the first thing that happens, and it causes all the subsequent events and brain degeneration. So a lot of

treatments are directed at amyloid, either removing it from the brain or preventing its formation, which is sort of what you would do if something bad is in there. You either get it out, or you prevent it from getting in in the first place.

And there are different types of treatments aimed at amyloid, but they've mostly been evaluated in patients with Alzheimer's dementia, people who have pretty advanced disease. Essentially all of them failed, and it's very discouraging for the field. One interpretation is, amyloid is not the problem. Yes, there's a lot of amyloid in the brain, but it's not really what's causing the problem. And there are many, many, many things that are wrong in the Alzheimer's brain besides amyloid. So some people think we should be trying to develop treatments targeted at something else, not just the amyloid. Most people still think that amyloid is the problem, but we're treating people so late in the disease, it's just too late. Even if you could remove the amyloid from their brains, their brains are so degenerated.

So, the field is now moving to earlier and earlier patients, patients who have mild impairment of their cognition but aren't really demented yet, trying to treat those people. They're also looking at people who have a

genetic form of the disease so they can identify those people very early, before they're even impaired in any way, but they just know they're going to get Alzheimer's disease because they have the genetic form. So they're looking at those people.

JS: And we can do that.

RGK: And we can do that. It does raise questions about if they're clinically well, but you know they're going to get Alzheimer's disease, how do you measure if the drug is working? Normally, we measure an Alzheimer's drug by patients' functioning or we give them a cognitive test and see they're better than they were on the drug, or better than placebo on the drug. But if you're fine, if you have no impairment, you're just going to get the disease in the future, the question is, well, what do you measure? Right? You can't measure their functioning; they're functioning fine. So maybe you should look at how much amyloid you're decreasing in the brain. Well, it's hard to know, for various reasons, whether that's going to help them down the road. So, as you go earlier, it raises new clinical trial questions: How long should the trial be? What should the outcome measures be? But that's where the field is going. The field in Alzheimer's is moving to earlier and earlier and earlier patients, primarily because

patients who have been treated with these drugs late, they haven’t worked. So most people still believe in the amyloid hypothesis, in other words, that amyloid is the problem, but the disappointing results have been because it’s just been too late and they want to go earlier and earlier. So that’s where the field is going.

JS: And it sounds like we need to know a lot more about the disease per se.

RGK: Well, that’s certainly true, that’s certainly true.

But I think everybody thinks if amyloid is the problem, treating early is a good idea. That just seemed to make sense, and let’s hope it’s true, but no one has shown anything yet in these early patients. They’re just starting to look at these patients. So people are hopeful, but they have been discouraged because of the failures.

JS: You spoke to changes in the division, but if you look a little bit farther out, look at the agency –- other than what we’re looking at now -- obviously this campus is one big change. But what would you put your finger on major changes in the agency just since you’ve been here, since ’83?

RGK: Well, again, probably the biggest thing has been PDUFA. I don’t know if that’s a change in the agency. I

mean, it’s had far-reaching effects in the agency, but I see it from the division’s perspective.

I would say it is more bureaucratic. Again, I think it’s because the law changes, we get new authorities, and they have to be somehow employed, and the agency has felt that there has to be new structures put in place. So, quite frankly, I think it’s a harder place to work than it was. It’s more micromanaged and it’s more bureaucratic.

On the flip side, we’re a smarter agency. I guess we’ve learned more about how to do things. But I do think it’s, I think we’ve sort of reached sort of a saturation point in terms of the bureaucracy.

JS: And when you’re using the word bureaucracy, are you talking about the structure of the agency overall?

RGK: Well, I’m really, well, in part, I guess. But I’m really talking about the structures that have been put in place to make sure that all the new authorities are handled appropriately across the agency.

As I say, every time we get a new authority or a new law, the new provisions in the law, there’s often a structure put in place that will make sure everybody’s doing it the same way. And so you’ve got to pass things through these committee structures before you can act on something, and that takes time.

JS: Well, when you make a decision as a Division Director, make a decision about a product to be approved, what happens to that decision? Once you come to that conclusion, where do things go?

RGK: Well, it depends on what the decision is. You know, there are some applications for which I'm the signatory authority. If a drug is already approved for something and a company wants to get that same drug approved for something else, I make the final decision on that. If a drug is a new chemical entity and has never been approved for anything, and they want to get it approved for something, my division reviews all the data and makes a recommendation to my boss, and my boss is the signatory authority.

JS: Who is that?

RGK: At the moment it's Ellis Unger. He is the Director of the Office of Drug Evaluation I. You know, there are three review divisions in ODE I, the Office of Drug Evaluation: cardiorenal, psychiatry, and neurology. For a new chemical entity in any of those areas, Ellis or Bob Temple, who is his Deputy, is the signatory authority. Bob used to be the Director and Ellis used to be the Deputy, and they flipped positions. So either Ellis or Bob is the signatory authority. But if a drug is already on

the market for something and they want a new claim, that's done at the Division Director level.

But I've got to consult with lots of people before I do it, in most cases, you know, for something major.

But, as I say, there's a post-marketing commitment or a post-marketing requirement, which is a new authority we have. There's a whole structure that you have to run your proposed action through or your letter through to make sure that the language is correct or make sure we're allowed to do this or that. REMS, of course, is a hugely labor-intensive activity. Pediatrics, which is a relatively new authority that we have to make companies do pediatric studies, a huge time and person-power expenditure. So all of these things are good, they're all useful, they are all very labor-intensive and very time-consuming, so it's that kind of thing. And, as I say, everybody brings a special expertise that's useful. But, as I said, with labeling, we used to sit around the Wang and bang out the label.

JS: Well, there are many levels that one has to deal with now as a Division Director than your predecessor.

RGK: Yes, definitely, without question.

And, again, as I say, it's useful, but it is, it does make things harder in that sense. You've got to plan better; you've got to do things earlier so everybody can

have their say. Yeah, it's just different. I guess a lot of people haven't been around as long as I have; they don't know that it was any different. But it was. But it wasn't necessarily better. It was just easier.

JS: Well, that might not be one of the things you missed, but looking back, what are some of the things you will miss?

RGK: I'll miss a lot of things. First of all, I'll miss the people. You know, look, it's a cliché. You spend more time at work than you do with your family, and that's mostly true. Right? So this is like my family. I mean, of course, people have come and gone. I'm the longest-serving person in the Division. But you see these people every day for years and years and years, some of them, years and years and years. I guess you could hate all of them and then it would be easy to leave. But I love these people. I look forward to seeing them every day. So that's the first thing I'm going to miss. I'm going to miss that.

And then, of course, the work. I mean, even though there have been many, many, many changes over this time, the mission is still the same. The idea is to get good drugs out there and keep bad drugs away from the public. So fundamentally, it's the exact same job, but we're better

at it than we were, much, much better at it. So I'm going to miss the intellectual stimulation both . . .

And I'm going to miss -- and this is related to both of the previous ones -- I'm going to miss the, just the interaction with people. I mean, as I said, I'm in meetings eight, nine hours a day so it's constant intellectual stimulation, but it's also social, you know. I mean, every meeting is sort of like an event.

JS: It depends on the person, I suppose. Some people would call that many meetings a day another stage of hell or something.

RGK: Oh, sure. And on one level it is. I come home and I am wiped out on a typical day, because it's physically draining. I mean, I'm not running around the room. I'm sitting and thinking. But, for whatever reason, the talking and the arguing, or just the thinking, whatever it is, it's physical, I find it physically draining. But you do it, it's the job. And it's all interesting. But it's also stressful because, as I say, you've got 60 minutes and you just want to pull the words out of people's mouths, some people. And sometimes the decision is hard. You know, you've got 10 minutes left, you've got five minutes left, you've got to make a decision, so it's draining. But it's incredibly exciting the job itself, in

meetings, whatever, they're all intellectually incredibly stimulating.

And then, of course, knowing that what you do affects millions of people, hopefully for the better. And I'm going to miss all of that.

I mean, the stress, I won't miss the stress at all, but I will miss those things. I will miss all of that. I'll miss the, not just the intellectual challenge, but the intellectually open atmosphere.

One story about Paul Leber. Another thing that I learned very, very early, I'd been here like a week or two. When you're brand-new, you go to a lot of meetings just to sort of get a sense of what we're doing, just to get a sense of what we're dealing with.

I came to a meeting. Obviously, I was the newest person. There were 10 people or whatever, staff who'd obviously been here much longer than I had. And Paul was running the meeting, and he said something, I don't know, whatever it was, and I disagreed with him. So I said, "Well, I don't think that's true; I think it's this." And then he said, "Well, no, it's this." And then I said, "Well, no." So we're starting to argue in the best sense of the word. I'm challenging him, he's challenging me, and I look around the room, and there's 10 horrified people

sitting around the room. And I'm sure they're thinking, "What's he doing? This guy just got here, he's antagonizing the boss. He must be a lunatic!" I don't remember anything about how it ended. I'm sure Paul won the argument. And I went back to my office.

I remember this very clearly. I closed my door. I said, "Might as well pack up." I said, "I can't believe did that." And at that moment he barged into my office, he just threw the door open, and he said, "That's fantastic! Nobody ever does that around here." So that's when I learned you should speak up, and the place thrives on argument, or it should, in the best sense of the word. Civil, but you say what you think, and you challenge people's assumptions and they challenge your assumptions, and you try to figure it out. So I'll miss that. I'll miss the arguing.

JS: I'm sure there's a good argument to be found somewhere in California.

RGK: I'm sure I'll find something, yeah.

So I'll miss all of that. I will not miss the stress, I have to tell you. There are many levels of stress, many reasons for stress, and I found them all.

But it’s been great, you know. I can’t even imagine working anywhere else, doing anything else, I mean, for a career.

JS: Sounds like it’s been a good run.

I want to thank you again for sitting down.

RGK: Oh, thank you.

JS: I’m sure that it will be a great addition to the corpus of interviews.

RGK: You know, it’s fun. I haven’t really sort of sat down and thought about the 30 years, so I appreciate the opportunity.

JS: Let me turn this off.

END OF INTERVIEW