



**Oral History Interview with  
David Jacobson-Kram, Ph.D.  
Director of Toxicology  
Office of New Drugs  
Center for Drug Evaluation and Research  
2003 - 2014**

**FDA Oral History Program  
Final Edited Transcript  
March 19, 2014**

# Table of Contents

Table of Contents .....	2
Oral History Abstract .....	3
Keywords .....	3
Citation Instructions .....	3
Interviewer Biography .....	4
FDA Oral History Program Mission Statement.....	4
Statement on Editing Practices .....	4
Index .....	5
Interview Transcript.....	6
Deed of Gift .....	30



## **Oral History Abstract**

David Jacobson-Kram spent much of his professional career in public service, conducting research in toxicology for the National Institute on Aging, the Environmental Protection Agency before joining the Office of New Drugs in the FDA's Center for Drug Evaluation and Research. In the interim, he also worked at the government contractor, Microbiology Associates, where he conducted research for regulatory submissions. In his oral history, Jacobson-Kram discusses the role of toxicologists in the drug review process, and their place in the Center for Drug Evaluation and Research.

## **Keywords**

DNA; Toxicology; Office of New Drugs; drug review

## **Citation Instructions**

This interview should be cited as follows:

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## **Interviewer Biography**

John Swann, Ph.D. is an Historian at the U.S. Food and Drug Administration. He is a subject matter expert in the history of the FDA, with a specialization in the history of pharmaceutical and biologics regulation. He joined the FDA in 1989, after earning his doctorate in the History of Science and Pharmacy from the University of Wisconsin, Madison, and researching a centennial history of the University of Texas Medical Branch at Galveston. He is the author of *Academic Scientists and the Pharmaceutical Industry: Cooperative Research in Twentieth-Century America*, as well as numerous articles on this history of therapeutic products published in scholarly journals and edited compilations.

## **FDA Oral History Program Mission Statement**

The principal goal of FDA's OHP is to supplement the textual record of the Agency's history to create a multi-dimensional record of the Agency's actions, policies, challenges, successes, and workplace culture. The OHP exists to preserve institutional memory, to facilitate scholarly and journalistic research, and to promote public awareness of the history of the FDA. Interview transcripts are made available for public research via the FDA website, and transcripts as well as audio recordings of the interviews are deposited in the archives of the National Library of Medicine. The collection includes interviews with former FDA employees, as well as members of industry, the academy and the legal and health professions with expertise in the history of food, drug and cosmetic law, policy, commerce and culture. These oral histories offer valuable first-person perspectives on the Agency's work and culture, and contribute otherwise undocumented information to the historical record.

## **Statement on Editing Practices**

It is the policy of the FDA Oral History Program to edit transcripts as little as possible, to ensure that they reflect the interviewee's comments as accurately as possible. Minimal editing is employed to clarify mis-starts, mistakenly conveyed inaccurate information, archaic language, and insufficiently explained subject matter. FDA historians edit interview transcripts for copy and content errors. The interviewee is given the opportunity to review the transcript and suggest revisions to clarify or expand on interview comment, as well as to protect their privacy, sensitive investigative techniques, confidential agency information, or trade secrets.

## Index

- benzene, 12
- biographical information, 6
- career
  - Director of Toxicology, Office of New Drugs, Center for Drug Evaluation and Research, 21
  - Environmental Protection Agency & George Washington University, 10
  - Environmental Protection Agency, Research & Development Division, 16
  - Johns Hopkins University Medical School, Oncology Center, 15
  - Microbiological Associates (aka, BioReliance Corporation), 18
- DeGeorge, Joe, 21
- drug development
  - animal studies, 27
- drug review
  - process, 25
  - role of toxicologists, 26
- education
  - National Institutes of Health, Aging Institute post-doctoral fellowship, 8
  - University of Connecticut, 8
- Environmental Protection Agency (EPA)
  - reporting, chemical manufacturing, 12
  - research program, 17
- FDA mission, 29
- General Services Administration (GSA), 28
- global drug registration, 23
- International Conference on Harmonisation guidelines, 23
- investigational new drugs (INDs)
  - drug review, 25
- Jenkins, John, 22
- Kweder, Sandi, 27
- Office of New Drugs, Center for Drug Evaluation and Research, 23
  - culture, 27
- research and instrumentation
  - designing studies, 16
  - DNA mutations, 9
- Temple, Bob, 29
- Toxic Substances Control Act, 11
- toxicology research, 19
  - chemical safety, 13
  - chromatid exchanges, 14
  - ionizing radiation, 11

## Interview Transcript

JS: This is an interview with David Jacobson-Kram. It's March 19th, 2014. We're on the White Oak campus in Silver Spring, Maryland. And, David thanks so much for joining us and participating in this oral history. What I'd like to start with, if I may, is where you were born and grew up and part of your early education and how you developed the interests that you actually carved into your profession.

DJK: So, yes, I was actually born in Stuttgart, Germany in 1949. And the reason I was there is my parents were Holocaust survivors. And so my father was released from Dachau and my mother from Auschwitz. And so they recovered in Germany after being liberated from the concentration camps. And once they had recovered, they got married.

And I had a brother two years older than me who has passed away. And so then much of my family had moved to Israel, those that survived the war. But my father and mother had large families. Most of them didn't survive. But those that did moved to Israel. And we were kind of late in leaving Germany. And the word that my parents got from their relatives in Israel is life was very difficult there because that was very early on. And things were very primitive. And so they counseled them that if they could emigrate to the United States, that would be a better choice than coming to Israel. So, my parents followed their advice, and we came over in 1949 on a troop carrier called the General Harry Taylor.

And so my parents, my brother, and I came over on this boat. My parents didn't speak a word of English. They had \$40, which they [unint.] into an empty tube of toothpaste because it was illegal actually to bring in American currency. But they were quite tenacious, very hard-

working. My father went to work in a factory. We lived on West 106th Street in Manhattan. But right from the beginning my parents were very dedicated to the notion that education was the most important thing for their kids. And so even they – they had very little means at that time. They sent both my brother and I to a private school, a yeshiva where we studied religion, Hebrew as well as English kind of studies. And so we lived there for a while.

My parents, you know, having survived the Holocaust, were fearful people. And it was kind of a strange childhood. I often think of it as like growing up on a different planet. My childhood being so different from other people's kinds of childhood. After living in Manhattan, we moved to Brooklyn for a short period of time. Went to another yeshiva. I was raised as an Orthodox Jew. So, you know, we ate kosher. We prayed every day. I wore a skullcap. And my father was a very religious man and studied the Torah every Saturday.

In 1959 we moved to Waterbury, Connecticut because my mother had a sister, also a Holocaust survivor, and her husband. And they were settled for some reason in Waterbury, Connecticut. And what's interesting is New York and Waterbury are about 100 miles apart. They didn't see each other for years because they couldn't grasp the notion that they could get on a train and see each other. But, finally they decided they were going to get together. And so we moved to Waterbury. Unfortunately, shortly after that my father died of a cerebral aneurysm. And so my mother then had to go to work to raise her two children. So, she had a difficult life. No question about it.

JS: So, you were about 10 and your brother was about 12 at this time?

DJK: That's exactly right. Yeah. And so we continued going to a yeshiva in Waterbury until eighth grade. My brother continued with his Hebrew education. He went to Yeshiva University High School in New York City and then Yeshiva University College. I kind of left the religion after my father passed away and went to public high school and the University of Connecticut. I majored in biology. The reason I was interested in this particular area is I was born with a very rare congenital malformation called primary femoral focal deficiency, which essentially means I have no left leg. And so I was interested in birth defects and how those things happened and what might cause them.

So, I majored in biology and then went on to graduate school at the University of Connecticut and studied embryology and developmental biology, having been very interested in that area. So, I had a very good graduate advisor in graduate school, almost like a surrogate father to me. He really took me under his arm and nurtured my way through graduate school. So, I did well in graduate school. My thesis was very well-received. After my presentation I got a standing ovation without a single question, which is pretty unusual. From there I went on and did a post-doc at the National Institute of Health (NIH) at the Aging Institute.

JS: So, this is in 1976?

DJK: In 1976 I finished graduate school and moved to Baltimore. The Aging Institute is one of the two institutes that's not on the NIH campus in Bethesda. So, the National Institute on Aging (NIA) is in Baltimore. The other one is National Institute of Environmental Health Sciences (NIEHS) which is in North Carolina. So, I spent four years there as a staff fellow doing research in the area of DNA damage and repair in aging.

So, there's a very widespread belief that what happens, why we age is because we accumulate the damage and mutations in our DNA because mutations are happening all the time. But we have enzymes in our cells that are capable of recognizing DNA damage. And when they see that, they're able to actually repair it. But the repair process isn't 100 percent effective. So, as time goes on, we accumulate more and more mistakes. And we accumulate mistakes even in those genes that are responsible for maintaining the integrity of the DNA. So, what happens is we become less and less efficient at recognizing and repairing DNA, and then that results in everything we associate with aging, grey hair, wrinkling skin, all these things.

So, the Aging Institute has some really interesting resources. They do a longitudinal study where they involve people at different ages in their lifetime and then follow them. They come in every year or every other year depending on their age, and they document all the physiological, medical, psychological changes. But you can also get tissue samples from these people. So, you can study, for example, the amount of DNA damage that's been accumulated over time.

They also have an aging colony of animals. So, you can get ahold of aged rats or aged mice and compare them to younger animals and again see how these things change as a function of age. So, it's a fascinating area, and you can definitely – you can document all these changes that occur with age. But the really hard part is to say well, is this really the underlying cause of aging or is it just another byproduct of aging? So, we can show that DNA repair declines, but is that why we age or is it just another symptom like grey hair or wrinkled skin?

JS: So, how do you test that?

DJK: That's a really hard one, and we don't have the answer to that yet. And people really are working very hard. But it actually, just from a logical point of view, does make sense since we can really see the fact that our ability to maintain the integrity of our DNA declines as a function of age except in, of course, in your reproductive cells because if you could imagine if that were true in germinal cells, then the human race would very quickly descend into nothing.

But our germinal cells are protected. And so they're different from our somatic cells, and their integrity is maintained to a much better extent, which isn't to say mutations don't occur there. A lot of them are lethal. Some of them are preserved, but in general they're much more efficient at maintaining the integrity of the DNA.

So, when I finished my post-doc, I then went on to a joint appointment. I was recruited by a professor who had just left Harvard, and he had taken a joint appointment between the Environmental Protection Agency (EPA) and George Washington University (GW). And so he recruited me into the same kind of position where I would work three days a week at the EPA and then two days a week in his laboratory.

JS: Now, was that unusual at EPA where staff had these kinds of joint appointments, an academic and a government appointment?

DJK: Very unusual. In fact, there were only three of us who were doing it. So, that was unique. And we did that. And he subsequently moved to Johns Hopkins University Oncology Center, and I followed him there. And so we continued in that joint appointment. And so, you know, I was doing basic research in the area of DNA damage and repair.

JS: Continuing with what you had done as a fellow.

DJK: It wasn't so much on aging because I didn't have those resources. I didn't have access to the longitudinal study or the aged animals. But the professor there I was working with was a radiobiologist. So, his specialty was understanding the DNA damage and repair associated with ionizing radiation. And so that was kind of related, and I continued along that track. And so we got grants, and we did research in that area, and we published a fair amount.

JS: So, I'd like to address a little bit about the work that you did at EPA. If you could characterize some of the review-type work you did and other studies or other responsibilities you had at EPA in that initial period because your title changed, and you started out your title was biologist in the toxic effects branch.

DJK: So, in the '70s Congress passed the Toxic Substances Control Act (TSCA). And this is kind of in the early days of environmental awareness. And the idea was to try to control the release of toxic substances into the environment, into the air, into the water, into the soil, and things like that. And up to that time really there was no regulation. So, if you wanted to make a new chemical, you went ahead and synthesized it. You could use it any way you want, and you could pretty much dispose of it the way you wanted.

So, TSCA kind of reined all those things in. So, there was a new requirement that if you were going to manufacture a new chemical, you had to notify the EPA. And we had – I can't remember how long it was, but something on the order of a month to review the information that

was associated with it. But it did not mandate that you do any safety studies. It only required that any information that you had had to be submitted.

And then EPA then had 30 days to either do nothing, in which case you would go ahead and synthesize your compound or if based on any information that we had, we felt that it really was a hazard, then we could stop that and require more safety data. That very rarely happened.

JS: So, the onus was on EPA to develop any evidence that might capture problems associated with these products?

DJK: Yeah. Kind of like cosmetics and nutritional supplements here at FDA now. The industry doesn't have to do anything. The onus is on us to show that there's a danger. They also had what they called the Section 4 Test Rule. So, for things that were already in the environment in large amounts like benzene, which is known to cause leukemia, we could force the industry to do certain safety tests.

But it was a very long and cumbersome process and would take years for these things to actually happen. So, essentially what we were doing, we were just in the initial stages of enforcing TSCA and figuring out how it was going to work and if it would work. And it's gotten better, but it's still – the onus is still on EPA. The manufacturer really doesn't have to do anything initially to demonstrate safety of a new molecule.

JS: Any of the reviews that you were involved in in this early stage, the first four years, does anything stand out as particularly remarkable or memorable, findings that you encountered that just kind of took your breath away or something like that?

DJK: Not so much. We had some really good folks. You know, back in those day – in these days there are really some sophisticated computer programs that do structure activity assessments. So, you can essentially dissect a molecule using a computer program and determine whether certain parts of that molecule are potentially reactive, whether they might interact with DNA, and that would send up a red flag.

Those things didn't exist in those days, but we kind of had human beings who were able to do that. So, we had some really good chemists and some really good physiologists that were able to look at molecules and say, you know, here's how I think this is going to be metabolized, and I think that's going to be a problem. So, we kind of did things, you know, we didn't sit in front of computer screens then, but we had some really smart people with great experience who were able to make really good predictions about whether something was going to be toxic or not. But then trying to enforce a test rule and to get the industry to actually do the testing was very cumbersome and very time-consuming. So, it's not a facile process by any means.

JS: Was there any connection between the work you were doing at GW and some of what you were doing at EPA? Could you tie any of those projects together in any clean way?

DJK: Yeah. What we were quite interested in in our basic research was trying to develop short-term tests that could be used to assess the safety or lack of safety of a molecule. So, for example, if you want to do a carcinogenicity study on a chemical, that is a protracted and expensive process. It uses hundreds and hundreds of mice and rats. It takes over three years to perform and costs many millions of dollars.

What we were trying to do was come up with short-term tests, most of them in vitro where you could essentially develop that same kind of information or at least use it as a screen to find out which molecules are going to be the most hazardous and which ones may not be and then you could prioritize the chemicals that you wanted to put through the long-term more definitive kinds of safety tests. So, we actually worked – I worked for many years on an assay called sister chromatid exchanges.

I can show you some examples, but the idea is that you looked at chromosomes through a microscope and by labeling them in a certain way; you could determine whether those chromosomes had been damaged by the test material. So, you would just – you'd take cells. Very often I'd just use my own cells, you know, get a blood sample. And grow them in vitro and then expose them to a test agent and then see whether the exposure caused an increased frequency of this event in the chromosomes.

And if it did, it suggested that that material was damaging the chromosomes and, therefore, was potentially carcinogenic, and that maybe should – would get higher priority for carcinogenicity assay or maybe even immediately, you know, take action on it and prevent human exposure to it or release it the environment.

JS: Was the nature of this work such that it was publishable work?

DJK: Oh, absolutely. Yeah. A lot of that is published. I published well over 100 papers in peer review journals. So, yeah, we did.

JS: I have to ask. You said this was kind of a rarity at EPA where scientists had a joint appointment. This was a fully joint appointment. You were paid by both institutions.

DJK: Got two separate checks.

JS: Right. So, what did your colleagues at EPA think of this that worked on this?

DJK: I don't know. I think it depended on the individual. Some people thought it was pretty cool and would have liked to do that also. Some people felt it showed a lack of commitment, you know. It's like well, we're here slaving away every day and why are you only doing this part-time? So, I got mixed reactions.

JS: By the way, were there any opportunities to teach or otherwise interact with the students at the school?

DJK: We were in the Oncology Center, which is part of the medical school.

JS: By the time you moved from GW to Hopkins you're talking about?

DJK: Right. And so I don't think I did anything in the way of teaching at GW, but at Johns Hopkins I did teach some – gave some lectures to the residents, medical residents on radiation-induced DNA damage and repair. So, I didn't teach a whole course, but just [inaud.] lectures.

JS: Did you enjoy that?

DJK: You know, I don't think I looked forward to it. I'd rather be in the laboratory than the classroom quite honestly.

[00:20:02]

JS: So, we're overlapping a little bit in periods here, but I did want you to say, if you would, a little bit about that you've had a change in position at EPA after you were a biologist there from 1979 to '83 and then through the rest of the decade your title changed. You were a geneticist. That was your position title. How did the government position change at that point for you?

DJK: Yeah. So, I switched divisions. So, I switched out of TSCA, and I moved into their R&D development division, which it sounds like they're really doing research, but they didn't because they didn't have laboratories there. But rather, you know, we looked at the kinds of assays that were being used to address potential adverse effects of chemicals.

So, like the kinds of assays that I described that we were doing at Johns Hopkins and GW trying to figure out what's the best battery of tests that we would use. If you're going to do like a flow diagram, what should you do first, and if that's positive, what should you do next, and so on? Then how do you do risk assessment? So, let's say you find out that a chemical actually does cause cancer in rats and mice, and then how to you extrapolate those results to risk the population?

So, if we find out that this chemical is in fact a carcinogen – take for example benzene, which is a well-characterized human carcinogen. And so we want to figure out well, just how dangerous is it to the human population? How much can you be exposed to safely? And if you're exposed to levels above that, how many people will come down with leukemia or lymphoma because of a certain exposure? So, we're trying to do kind of quantitative relationships, which is a challenge. So, in that sense my responsibilities changed and the focus was a little different.

JS: Research seems an essential element of what EPA does. Understanding, of course, that you were not necessarily in the position to get involved in budget decisions and so on – or perhaps you were. I'm not sure. But did you get the sense that this was something, that this core responsibility was something that Congress understood and recognized in terms of getting the funds that labs like yours needed to do to carry out the responsibilities of the agency?

DJK: Well, our funding for the labs at GW and Johns Hopkins came from NIH, not from EPA.

JS: I'm talking about the work at EPA per se because obviously there's research going on there too.

DJK: Now, EPA does have labs, but they're located in North Carolina. And so their mission essentially is to support the regulatory function in Washington, D.C. So, and they do. So, if there is a new assay pending or a new endpoint that looks promising, the mission of the labs in North Carolina is to develop those assays so that they can be used in a regulatory context.

JS: Is the lab there anywhere near NIEHS?

DJK: Right across [unint.] from each other

JS: So, in it was about 1988 that your career track takes a pretty substantial change. This academic career track, this government career track. You take on an executive position in a company called Microbiological Associates. So, I wondered if you could talk a little bit about what led to this decision and what it was Microbiological Associates did.

DJK: So, Microbiological Associates, it's an interesting company if you look at its history. It was founded in 1949, and it was really – it was organized initially to produce reagents for cell culture. So, they would make cell culture media and things like that. But it kind of evolved. And mostly they did government contracting. So, probably 90 percent of their revenue was government contracts.

But it evolved over the years. It was a private company. It was then purchased by an individual. And the reason [unint.] was to develop an instrument for veterinary labs that would diagnose certain kinds of viral infections in laboratory animals and also in companion animals. The technology though wasn't quite up to it. And so they made some of these instruments. They sold some of them. They didn't function very well, and the company was kind of floundering. And so they decided to kind of fall back on things that they knew, which was doing government contracting and doing toxicology and things like that. So, I came in there in 1988. They recruited me to be head of the genetic toxicology division.

So, what that division did was they would do GLP-type studies for regulatory submission either to EPA or FDA or to European or Japanese regulatory authorities. And so we would do things like the Ames test, which looks at gene mutations or look at chromosome breakage assays or unscheduled DNA synthesis, which tells you if a material is causing DNA damage. And then you'd write a report, and that would be submitted to the regulatory authorities. So, what was going on, and I didn't quite realize this, is the company – the previous director of this division had gone and joined a competitor, who at that time was [inaud.]. And what he was doing is he was poaching all the really good people from Microbiological Associates.

So, they recruited me, and it was really a very, very difficult choice, and I really – I labored over this tremendously. But my wife was very supportive, and we'd walk around the streets in the middle of the night, and she helped me decide that this was really something I should try doing. It was very different from anything I'd ever done before. I had no business training or anything like that. So, I joined there. And at first...

JS: Where are they by the way?

DJK: Rockville. The first year was incredibly stressful because people were like leaving and I had to keep replacing them, but we got through it. And ultimately that division thrived. I was very lucky that I was able to recruit really, really good people. Our revenues and our profits grew. And we went more towards commercial studies and much less away from government contracting.

So, I learned a lot about business, and my responsibilities kept increasing. So, initially I was only in charge of the genetic toxicology program. Then they expanded that to the animal

toxicology program. And then finally to their diagnostics looking again – there was another business looking at serology of laboratory animals.

So, I was there for a total of 15 years. And when I joined the company, probably total revenue for the whole company was under \$20 million. And by the time I left, revenue for the division that I was responsible for was well over \$20 million. So, I was very fortunate things worked out very well.

JS: It's very different though. Did you miss the lab and the sort of work you had been doing before that?

DJK: Well, you know, up to that point I spent hours and hours just staring through a microscope looking at chromosomes. I was pretty much ready to move away from that microscope and do other things, and it was fascinating because, as I said, I walked in there, you know. I didn't know anything about gross margins and operating revenue and things like depreciation. But that was pretty interesting. And I think I was really able to improve just about every business aspect of the division.

So, our revenues grew, our margins improved, operating income improved. And I have to say in response to it the company was very generous to me. So, by the time I left, I was making more money than I am now having been here for 11 years. And, you know, we'd get bonuses and stock options, and the company did go public eventually. And so it became known as BioReliance Corporation. So, that was a financial boon for me since I had stock options which then materialized. So, when I finally came here, the financial sacrifice wasn't so bad because I had a little bit of a nest egg that I built up in private industry.

JS: So, describe how it is you came to FDA and who recruited you and what the position is all about and why it attracted you.

DJK: So, to me that's really kind of an interesting turn of events. So, I'd been there for 15 years, and things went well. But I have to say; over the course of 15 years I really drifted away from the science and just got to be more of a financial person. So, I was, you know, talking to the board. I was putting together budgets, you know. And the science was becoming more and more remote. Then the position that I occupy here, my predecessor had left, and he went to Novartis. So, he became the chief toxicologist there.

JS: And who was that?

DJK: Joe DeGeorge. And there was this opening. And essentially this position that I'm in as the head of toxicology for Center for Drug Evaluation and Research (CDER). So, that was always an interesting position because being at BioReliance, you know, we would submit protocols to FDA. And then they would be evaluated by the Executive Carcinogen Assessment Committee, and Joe DeGeorge was the chair of that committee.

And really he was the spokesmen for toxicology for the Center of Drugs. And that was always kind of a cool position I thought. If you're going to be in toxicology, that was, to me, kind of the best thing you could do. So, a colleague said, you know, there's an opening at FDA. I think you should apply for it. So, I said oh, what the heck. I'll put my CV in because traditionally they would hire from the inside.

So, you know, if somebody left like Joe DeGeorge, you know, he'd have some [unint.], and they'd usually choose somebody from [inaud.]. That happens here quite often. So, it would be unusual to hire somebody from the outside into that position. So, but I put in my CV, I interviewed, and they selected me. I was actually quite surprised but very gratified. But that was a little scary too. That was another big transition. I'd seen the other side of drug development, you know, working for sponsors. But not from the regulatory side. But I was very fortunate. The people here were very welcoming, very supportive. My boss is John Jenkins, who you may know, and I got to say, aside from my graduate advisor, the best person I ever worked [inaud.] really smart, hands off, you know, doesn't stare over your shoulder, very, very smart and just a pleasure to work for.

JS: So, how is it that the toxicology component here is within the Office of New Drugs as opposed to Drug Safety, say the Office of Drug Safety?

DJK: Yeah. You know, it's kind of an evolving picture. We have these review divisions that focus on particular areas like cardiorenal, neuropharm, things like that. And it used to be that they were like little fiefdoms unto themselves because they would have their own chemists, they had their own toxicologists, and they'd have their own clin pharm people. And with time these disciplines broke away from them. So, chemistry became its own office and with its own hierarchy. They still worked with these divisions, but they weren't part of them. And the same thing happened with clin pharm. And I actually tried very hard to do the same thing with toxicology, but I have to say that was one of my big regrets that I was never able to accomplish that.

JS: So, there's some centralization then of functions.

DJK: Yeah. So, right now within OND within the review divisions you have the clinicians, you have the project managers, and you have the toxicologists. All the other disciplines are offices unto themselves. And what I try to do is do the same thing with toxicology, but too much resistance.

JS: So, obviously your focus has been on toxicology here, but over the past decade what sort of major shifts have you seen within the Office of New Drugs?

DJK: One of the responsibilities that I have in this position is I'm the lead safety person for ICH guidelines. And ICH guidelines is the International Conference on Harmonisation. And we meet three times a year. And [unint.] is to put together guidelines so that if a pharmaceutical sponsor follows these guidelines, their studies will be acceptable in Europe, the United States, and Japan because before ICH every region had their own guidelines.

So, if you wanted to get a drug registered globally, you had to do theirs, you had to do ours, and it was very inefficient. But with the establishment of ICH, what we said is okay, we're all going to get together. It's going to be contentious, but we're going to agree on one way of doing this, and if you follow that way of doing it, we're all going to accept the results of those studies. And so I've been part of that process for 11 years now.

And for me, that was very gratifying because it makes registration of drugs globally much more facile. It reduces animal usage because you might imagine that one region would

require, let's say, 50 animals per sex per dose and another one might require 75. And so if you had to do separate studies for each region, you were using animals needlessly or you had to inflate the protocol so that it fit everybody's requirements. But, this way things became much more streamlined, and we were able to make things much more efficient. And so with our guidelines for safety, which is basically toxicology, for efficacy, which is basically clinical, and chemistry. So, for chemistry manufacturing controls (CMC) issues.

JS: It's a terrific end result to have unification of standards among the regions, but my guess is it's not always so easy getting to that point. And I wondered if you could narrate how, you know, some of the struggles one faces when trying to achieve these agreed-upon guidelines in the three regions.

DJK: Yeah. So, it sometimes can be very onerous. And the reason is that you bring together these folks, and the attitude usually is well, I have always done it this way. And it's always worked so well for me. Why should I adopt your way of doing things? And so it requires a tremendous amount of compromise. And, you know, as I'm sure you're aware, people vary in their ability to compromise. It depends on kind of their personality. So, these things don't happen quickly. We have to meet quite a few times. We have to have quite a few telecons, emails, but we always – finally we get to it, you know. At the end of the day it usually takes between two and three years, but we come to an agreement. And everyone doesn't get everything they want, but we compromise. And I think the results in all those areas have been really positive. I think it's been good for drug development. I think it's been good for patients.

JS: So, as you kind of look back at the time you've been here – you're about to move on to another phase in your life, but as you look back, how do you see things – how might things be improved? Where can we make some changes in the programs you've been involved here in the agency?

DJK: You know, one of the biggest challenges of anyone in this position, and this was made clear to me at the time that I was interviewing, is as I kind of indicated before, the different review divisions operate very independently like siloes, if you will. And that's a problem because they have their own ways of doing things. We've always done it this way, and it's always worked well for us. But they can be very different from each other. Some have a reputation for being extremely conservative and requiring mountains of data.

Other divisions have a reputation of being more flexible. So, one of the biggest challenges of anyone in this position is to try to bring consistency between the divisions. So, what often happens is a sponsor will submit investigational new drugs (INDs) [ph.] to two divisions or three divisions because they don't really know what – they have a target, but they don't really know what the indication is going to work best for. So, they do a shotgun approach.

They put INDs [ph.] into different divisions. So, maybe it will work for this, maybe it will work for that. But that's not unusual. And sometimes it works for many things. So, it isn't always just a fishing expedition. But the reaction of the divisions could be very different. Some divisions, they look at the same set of data and say well, you can't put this into healthy volunteers. And others say ah, that looks enough. So, then it's kind of the responsibility of the person in this chair to try to get them to agree on, you know, is this really okay or not.

So, I believe at least in my tenure things have improved, but I wouldn't say that we have 100 percent consistency.

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JS: Maybe what these people need to do is spend some time on the ICH to learn about compromise.

DJK: Yeah. But you see, one of the reasons that I favored having a toxicology office is right now the people in the divisions identify with their divisions. Okay. So, it's not that I'm the toxicologist; I'm in the neuropharm division or I'm in cardiorenal. What I wanted them to do is to identify with being a toxicologist in OND. And this is how we do things as toxicologists in OND, not how toxicologists do things in psychiatry.

That way I think that was a way to get consistency, but that didn't happen. We have made some progress. The other thing that I've tried to impress upon people is really to be very judicious in their requirements for animal studies. Animal studies help us in drug development, but I don't want reviewers to be box checkers and say okay, I got to do this, this, and this because, you know, if that's all we do, we don't need Ph.D. toxicologists to determine if a box had been checked.

I want them to sit down and say why do I need this study, and if I ask for this study and it comes out this way, how's that going to affect development of that drug? And if the answer is, you know, I'm just curious; I really want to know how that comes out, that's not an acceptable answer. It really has to have some impact on drug development. If not, don't just ask for a study

to satisfy your curiosity because just because you're not in the lab anymore, this isn't a way of getting a study done and satisfy your intellectual curiosity. We have to be very respectful of how we use animals in drug development. So, I think I've gotten that message across in the time that I've been here, and I think we've gotten a lot better about being thoughtful before asking for an animal study that maybe you can do without.

JS: Well, if the person who's heading toxicology in the Center for Drugs says that, I would think that would have some weight.

DJK: I think it has. Yeah. I think the message has really gotten out that we're in favor of the three R's and that we look forward to a time when we can do drug development without animals.

JS: You mentioned several people along the way and you pointed them out here in the agency. You mentioned John Jenkins. Anyone else you've had contact with over the years on an ongoing basis that has had a particular impact on the way you do things or look at not only your job but the agency overall and the role of FDA in American society?

DJK: Yeah. There are so many. There are so many good people here. There really are. I wouldn't, you know, it's like any organization. Not everybody is a star here, but unfortunately government employees really do get a bad rap. We have some really brilliant people here at OND. So, it's been a real pleasure to work with John and his deputy, Sandi Kweder. Also just a pleasure to work with over the years the division directors, the [unint.] directors, the other supervisory toxicologists. All really, really good people. Many of these folks could just walk

out the door and double their salary in industry, but they hang in there and they do their job day to day.

And as you've seen, you know, we're making it harder and harder for people to be government employees. I used to have a great office down at the end of the hall that was about twice this size, but then the General Services Administration (GSA) decided that the square footage for [unint.] was overly generous. You know, I haven't had a pay raise in three years, right. And just this notion that we're just a bunch of lazy, you know, freeloaders. It's really unfortunate. And that isn't to say that everyone here is a star, but people here really take what they do very, very seriously. They make important decisions. And by and large, you know, you can't be right all the time. And so we get hit from, you know, you're doing things too fast and recklessly or you're taking way too long and...

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JS: So, I haven't asked anyone this before in an oral history, but you bring an interesting perspective here. You've had a pretty substantial career in government, in the private sector, in academe. So, let's say you were going to go talk to a group of new hires in FDA. I mean not just people in drugs, people in tobacco products, and the Office of Information Management, and [unint.], all over the place. So, this is a nice cross section of people in the agency. And so you're going to give them a brief talk about public service. You touched on this in what you just said, but what do you think they should know about the importance of public service?

DJK: I think what you really have to do is understand what our mission is, and you have to really be – you have to identify with that. And if you can't do that, you don't belong here. You have to – you really have to believe in that what we're doing here is protecting the public health, improving the public health. And if you're just looking for a 9 to 5 job and watching your paycheck appear every other Friday, this is not a good place for you.

We do have some people like that, but I mean, you know, the real stars in the agencies are those people who do this. I mean, you know, you look at somebody like Bob Temple. He's spent his entire career doing this. And, you know, Bob Temple obviously could walk into any pharmaceutical company and be a millionaire, but he doesn't. He takes this job really, really seriously, and he loves it. He just – he looks forward to coming to work every day.

And those are the kind of folks that we need. And it's a unique kind of person because, yeah, you know, there are benefits for working to the government. The starting pay actually for somebody coming in as a toxicologist compared to industry is not so different. Now, the ceiling is much higher in industry. So, for a senior person you're making considerably less. But, you know, as a starting salary it's pretty decent. We have good benefits. But that's not a reason to work here. You really have to believe in our mission. That's what I would say. And certainly the Center for Drugs, it's an important mission.

**END OF INTERVIEW**

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