

**History**  
**Of the**  
**U.S. Food and Drug Administration**

**Interviewee:** John E. Simmons, Ph.D.

**Interviewer:** John P. Swann, Ph.D.  
Robert A. Tucker

**Date:** June 6, 2006

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Interview with John E. Simmons, Ph.D.

June 6, 2006

TAPE 1, SIDE A

RT: This is another in the series of FDA oral history interviews. Today, the interview is being conducted with Dr. John E. Simmons, former Director, Division of Pre-Marketing Assessment and Manufacturing Science, Office of New Drug Quality Assessment, Center for Drug Evaluation and Research. The interview is being conducted in the Parklawn Building in Rockville, Maryland, on June 6, 2006.

In addition to Dr. Simmons is Mrs. Gail Simmons, his wife and our transcriber at present for the FDA Oral History Program; Dr. John Swann; and Robert Tucker of the FDA History Office.

John, as we begin, we like to get some personal history, where you were born and educated, and so on, and then, later, move on to the career with FDA. So we'll let you begin that way, if you will.

JES: Well, certainly, thank you. By the way, I'd like to thank you for the invitation and the opportunity.

Originally from the East Coast, born in Philadelphia, and I was the first American-born male in my family to graduate from high school, and I went on. I came

from a working-class family, so my career, my higher-education career didn't start initially. I was actually a licensed electrician and built homes for a while.

I thought that might raise an eye.

Then I started school, and I worked my way through school as a professional musician. I had a jazz quartet and played up and down the East Coast, and that financed my college education because my family had limited means.

JS: What did you play?

JES: Guitar, bass, and piano, and I enjoyed it. And I've told people kind of as a joke, I think I'm the only career FDA'er who has published in the scientific literature as well as *Downbeat* magazine.

JS: Before you go on, let me just ask, was your family musically inclined?

JES: No, no. I think I was the only one who ever pursued it with any, at least any financial help. But my family was a family of immigrants and they worked in places like aluminum-ingots manufacturing, things like that. They were salt of the earth.

At any rate, I also have something on my resume that a lot of people don't have, and that is that I served my country during the war, was overseas for a while. And I guess what I've got to show for that is a couple of, a few years of retirement. But when I came back, it did pay for my continuing education, which was nice.

JS: You did security work, I gather.

JES: I was in military intelligence, and I was in encryption and did some things that I really don't talk about much. It was wartime and I was overseas, and that's all water under the dam right now.

RT: What were the years or what was the war?

JES: It was the Vietnam War. And I was in from '69 to '72.

At any rate, I came back and went on to graduate school, did my graduate work at the University of Pittsburgh, School of Pharmacy in pharmaceutical sciences. And I actually stayed on there and taught for a while before I wrapped up my dissertation and defense.

RT: You did your undergraduate work at Temple. Is that correct?

JES: Yes.

RT: What was your degree from Temple?

JES: Original training, the early training was in chemistry. But I did a cooperative program with the School of Pharmacy, which was just up Broad Street. So I took courses in both chemistry and pharmacy.

JS: What attracted you to science, not necessarily pharmacy in particular, but science?

JES: I've always been fascinated with the human body and its interaction with molecules, and medicines were a natural draw. What makes a medicine do what it does in the body, and what's the structural requirements for that? It's fascinating.

RT: When you received your degree in chemistry, then you're then involved in instruction. Is that correct?

JES: That's right.

RT: Did you ever actually enter the employment market in the chemistry discipline?

JES: Never did, never did. I went into academia and stayed at, as I said, Pittsburgh for a while, and then I went out to the University of Kansas, School of Pharmacy.

You're from Kansas.

JS: I was at Kansas. I was a history and chemistry major.

JES: Really.

JS: I spent many hours in labs at Malott Hall.

JES: Interesting.

JS: I was there from 1975, when I started, until 1979, when I graduated. So I just missed you.

JES: Just missed, yes.

JS: But I wanted to ask a question about your experiences there.

JES: Sure, sure.

JS: Which is, you were at the School of Pharmacy there. Did you have contact with Take Higuchi?

JES: Oh, sure. Take had laboratories right across from mine -- we were out on the west campus, the Smissman Research Group.

JS: Take Higuchi is the father of physical pharmacy.

JES: Yes, he is, he is, the godfather. And an active one. He was a driven, bright guy. He had this brother Bill, who actually was up at Michigan, I think still is, and Take and I



used to have discussions. I don't think we ever worked on anything together. He was interested in other things, but, yes, we were right across the hall from one another, so I saw him all the time.

He had a heart attack, so he was in the process of recuperating and cutting back. And he used to run; he was an avid runner, and he had to kind of wean himself back into that and start walking. I think he got to the point where he ran.

He died not too long ago.

JS: Right.

JES: His wife is still out there.

JS: He had many students.

JES: Oh, yes, just a steady stream, probably trained more people for the pharmaceutical industry than any other.

JS: I would gather, one of the more active members of the school. Right?

JES: Very prolific. I can't tell you how many hundreds of things that he's published. But he was just very prolific and very, did some seminal research. I mean, he laid groundwork.

JS: How would you characterize your research when you were there?

JES: Sure. I think it was very much in the drug-discovery and preliminary-screening mode. That's what I was doing. I was looking at drugs, neuroleptic, drugs for neurological application and had a small group. I had some grants.

I had -- probably fairly unusual out there -- got some money that came through the back door. By that, I mean that the Defense Department was interested in some of what I was doing. I was looking at cholinesterase inhibitors and things like that, and I got quite a bit of grant money for that research and published some very nice work.

We had a very, very fascinating thing that we discovered. It was, I'm not going to say it was serendipity, but it was one of those things where sometimes you venture into areas that you don't have a lot of formal training in and you succeed despite your lack of knowledge, and that's what happened.

We took plastic polyethylene beads and then chemically linked enzymes to it. And we could screen drugs by washing the drugs through a column of this immobilized enzyme to see where it bound and where it didn't. It was a fascinating idea, and it turned out to be interesting work.

RT: Now, was that -- according to some information you have provided -- about in the period of 1980 to '83?

JES: That's right, that's right.

RT: When you were at Kansas?

JES: Right. And that was enjoyable; I enjoyed that.

JS: Now, certainly we want to get you to FDA.

JES: Yes.

JS: Had it ever occurred to you to work in a regulatory agency? What brought you to FDA, what contacts or what situation?

JES: It was interesting. No one trains to be a regulator, no one. I mean, there were no regulatory science programs. I would love to write the curriculum, and I hope to do that, quite honestly. I'm working with a couple of schools of pharmacy right now.

I had a colleague that was in Pittsburgh. He came down to the D.C. area and started working for the agency. And he called me up one day and he said, "John, this is something that might interest you. You might want to try it."

So they put me in touch with the Division of Biopharmaceutics at the time and said, "Why don't you bring him in, see if you like him, and I think he'd fit in." That's what happened. I came down, I interviewed. They looked over my resume and said, "We can use you. Would you like to join the government as a regulator?" I said, "What do I know about regulation?" That's what happened.

So I went from Kansas to suburban Maryland and started right in reviewing the applications that . . . At the time, it wasn't CDER, it was the Bureau of Drugs, Center for Drugs and Biologics.

JS: Right. That's in Biologics.

JES: That's in Biologics. That's right, they were together. Here we are again, back to where we started.

RT: Who was the person who you interviewed with? Do you recall?

JES: Bernie Cabana was the guy that headed up the group. He started the biopharmaceutics group here. And Jerry Skelly was his deputy. And I joined. And Bernie promptly left and started his own business, and Jerry took over. And I worked for Jerry for, I don't know, about three and a half years, somewhere in that vicinity.

And it was interesting because the way they attracted me was they said, "Look, you can continue to do some research down here." That's the connection with C Street. That's where our research laboratories were. We had animals, we had supplies, and we had laboratories. Charlotte was down there.

JS: Now, when you say C Street, this was the old Federal Building.

JES: The old Federal Building down there at 2<sup>nd</sup> and C. It's right behind where the Commissioner sits and right across the street from the Sam Rayburn Office Building and Independence Mall.

As a matter of fact -- this is a true story -- I was walking from C Street to train station one evening, a summer day, and as I'm going across the Capitol grounds, which you probably can't do now, they had the news trucks up with their antenna and the portable transmission towers, and here the newscaster is talking about the news of the evening and they're all wearing shirts and ties and sports jackets, and below they had shorts and sneakers, because it was hot.

At any rate, I'm walking towards the train station, and lo and behold, I see Senator Nancy Kassebaum, who is my representative from Kansas, walking across the street to the Dirksen Office Building. So I walked up to her -- she was wearing a purple dress -- and I introduced myself. And she said, "You know, I don't run into too many of my constituents up here." She said, "Would you care to join me in the office?" So I walked with her into her office, and we sat and chatted for fifteen or twenty minutes. She just wanted to know what I was doing down here. She was a delightful person.

She was the daughter of Alf Landon, the governor of Kansas.

RT: Alf Landon, right.

JES: He was very loquacious.

RT: I remember back in the election when Alf Landon was a Republican nominee, and, of course, the only state that he carried was Kansas. And so the school boys -- I was about ten years old -- the boys in the schoolyard would pull what they thought was a joke. You'd ask, "Why does FDR always take the train?" and, of course, the answer was, "He was afraid of Landon." It supposedly was why he never flew but always took the train.

Well, it turned out he didn't need to be afraid of Landon.

JES: He was legendary out there. But his daughter really did some nice things. I thought she was a nice lady. She didn't have that mean nastiness that we're hearing today, not quite so partisan.

But the Midwesterners are generally like that. I think they tend to be a little less strident, a little more reserved.

RT: I think so. It's a softer part of the country.

JES: I think so, I think so.

But I loved living there, I loved Kansas. And I got up to Nebraska, Oklahoma, places like that.

So I came to the agency. That was the nexus. That was interesting.

JS: Now, when you arrived, what sort of training did you have in regulatory work?

JES: Zero. I was given, at the time, the *Code of Federal Regulations* and asked to read them, and that was the extent of it. There weren't any training programs, there were -- I don't even think they had the law courses that they have now. Now they've got food and drug law, you know, basic, advanced, they've got some specialized classes. I've taught some of them. I find it fascinating how much better we've gotten than we used to be.

RT: Just to kind of put in perspective where you were . . .

JES: This wasn't that long ago; we're not talking about that long ago.

RT: To put into perspective perhaps your experience at that point.

I don't think we mentioned when you actually got your degree at Temple. Did we give the date on that? I think you were a teaching graduate assistant between '73 and '75.

JES: Right.

RT: That was after you received your degree.

JES: Right.

RT: Which would have been about '72 or so?

JES: Yes, right.

So I went from Temple to Pittsburgh, and then went out to Kansas.

JS: So we have your bachelor's degree in 1973; your master's degree at Temple in 1976; and your Ph.D. in pharmaceutical and medicinal chemistry from the University of Pittsburgh in 1980.

JES: And it's interesting. At Pittsburgh, I had the privilege of working with, at the time, a Pittsburgh Pirates star first baseman, Willy Stargel, whose daughter had sickle cell anemia. And we had a very extensive cooperative program that he helped fund on looking for agents to try to ameliorate the symptoms. We can't cure the disease, but you can ameliorate the symptoms.

When the hemoglobin starts to gel and the red cells take on irregular shapes, they clog the capillaries, and that's very painful, it's very tiring, it's very exhausting. And his daughter was sick with that, and he moved mountains to get us some money.

And it was fascinating, because we used to have to, I used to have to take sickle-cell patients during their remission phases, where they weren't experiencing a crisis episode, to draw blood from them so that we could use small amounts of their blood to screen some of the things that we were looking at. And it always touched me very deeply to see some of these young folks come in and willingly donate a few tubes of blood that we would precious use to screen some of the agents that we were looking at, designing. And I developed a very, very deep respect for people that are willing to get involved in medical research as donors. It's fascinating.



JS: Just out of curiosity, were you able to come up with anything?

JES: We were. But the one problem with diseases like sickle cell anemia is -- and this is something you might understand -- concentration. We have a lot of blood in us, but it's on a large scale. It's a huge amount of hemoglobin -- it's a huge concentration that's circulating in the blood. In order to get a drug in there to affect enough of the molecules requires a Herculean amount of material, and we never could get across that barrier where we could deliver enough drug to suppress the gelation to the point where it wouldn't cause crises. They've tried lots of things that will interrupt that process, and it's always the same problem. You need so much drug circulating in the blood that very often you just can't get enough into the red blood cells. So we had agents that were very active when we took the cell membrane away, but when we went to whole blood and circulating serum, we found that we simply couldn't maintain the levels that we needed to suppress that gelation in the whole blood. So we were partly successful but we weren't wholly successful. We never got anything that really would have become, I think, an effective drug. And to this day, there's still nothing.

Now they're approaching it genetically. They're trying to turn on some of the genes that would allow normal hemoglobin and fetal hemoglobin, one or the other hemoglobins, to start being incorporated into the red blood cell, and I don't know where they're at with that. It's fascinating.

JS: I want to just see where this goes, and we'll get into some of the details of what you were doing specifically in each of the offices. But you mentioned something, that

when you arrived here, you were told that one of the things you'd be doing as a regulator was research.

JES: Yes.

JS: Can you tell me if that promise was fulfilled?

JES: It was.

JS: You were in the Center, the combination Center of Biologics and Drugs, and later they separated and eventually became the Center for Drug Evaluation and Research.

JES: Right, right.

At the time, some of the hot topics were, revolved around -- and, by the way, I'd like to editorialize it a little bit. This is one of the few agencies that I know of where the law does not clearly define what a drug is, what a toxic impurity is. Most of that has to be established by scientific study to look at. We approve drugs because, as a corporate group, all of the disciplines must come to the realization that it's safe, that it's effective, that the formulation can be reproducibly manufactured and delivered, and there's no guiding principle other than good science. There are requirements for the numbers of studies, the types of things that have to be submitted. But the ultimate approval of a drug requires scientific judgment by people like us. And I find that fascinating. Not too many regulatory agencies where you see that.

RT: The agency's move toward doing research is relatively recent in its history.

JES: You're right, you're right.

RT: Because I think initially, the regulatory agency looked to the pharmaceutical companies to do the research.

JES: That's right, and we still do. We can't possibly compete with them on that.

But at the time, some of the issues were rather interesting and revolved around formulations.

When I first joined, there wasn't the type of cooperation we see now between the European community, the FDA, Japan, Canada. We were finding that companies would have different formulations or even different doses of the drug approved here in the United States, in the various European countries and Canada, in Asia, and what one of the interesting things was, was the science of the formulation. Why did we approve the formulation we approved here, and how did it compare to some of the others? So we did an awful lot of formulation comparison. The requirements for dissolution testing of products really didn't start till about the 1975 or '76 USP. Okay? That's 30-some years ago.

RT: Was the USP sort of the lead coordinating organization?

JES: The USP is an independent, nongovernmental standards-developing agency, and it's recognized in the Act, so we're intimately linked by that Act. The USP, the U.S. Pharmacopeia, and the FDA have to work together. Whenever the USP is going to add an additional drug to their compendia, we always review it. We compare it to the NDA that we reviewed and approved here, and make certain that there's no gaps, nothing falls through the cracks, there are no grey areas, that it's crystal clear, because once it becomes compendial, then that's the gold standard. Anyone who picks up an aspirin, goes to the USP and tests it for aspirin content, they look at how it's screened, how it dissolves, how it disintegrates. So the requirement for the agency, and the Center for Drugs in particular, work very closely with the USP. It's always been there, and I've been involved in that. So some of that research was cooperative.

JS: That's good. But if we're finding various international standards for something like dissolution rates, now, how do you get the USP and the British Pharmacopeia and the other compendial standards around the world to come to some harmony on standards like that?

JES: Harmony is the key word. I'm sure you've heard of the International Conference on Harmonization, ICH. It's been the avenue for that, and I've been intimately involved with that ever since it started back in the early '90s. It was a wonderful idea.

The United States, the European Economic Community, and Japan, the big three, we started meeting on a formal basis to come up with guidelines that would cover the minimal content that we felt was critical scientifically and compendia were one of them.

Harmonization of compendia was part of harmonization around the world on the content and the format of applications. So it's been fascinating, it really has.

And I don't think that's a static effort. It's a dynamic effort. It's ongoing as we speak, and I hope that it continues. It would be awfully nice to see a formal set of guidances and guidelines that all the countries look to as the gold standard of what's required both in the chemistry and the manufacturing, in toxicology, clinical and safety testing. All of that is being standardized as we speak by committees of scientists from around the world, and I've been involved in that. It's fascinating. It's just fascinating to see the differences of opinion. I'll give you an example.

Because of the thalidomide event here in the United States, our gold standard was always placebo-controlled trials, where patients would get the drug and other patients get a dummy drug, and we'd compare those two population groups. Well, in Europe, they feel that's unconscionable ethically; they don't like to see that. So what they like to do is comparative studies where they look at another drug that supposedly treats that same condition and compare the two. There's a strength with both approaches.

With the placebo-controlled study, you know that any change that you see has to be attributable to what you give the patient. In Europe, you assume that the first drug you're comparing it to has the same effect, and if it doesn't, it's difficult to interpret.

So I think there's room for both, and I think it's something that we're hashing out right now as we speak.

JS: One of the great concerns when the 1962 amendments were passed, of course, is that the industry was promised that this would not involve comparative studies, particularly of drug effectiveness.

JES: That's right.

JS: And so that movement that you just described kind of flies in the face of that element of history of drug regulation.

JES: That's right, that's absolutely right. And I'm not going to discuss the ethics of it, but I'll discuss the science of it.

If I were testing an oncology product, that is, a cytotoxic agent, would I want to do it as a comparator scientifically, or would I want to compare it to no drug? I think the trouble with comparator trials is that you can't always assume that these two drugs have the same mechanism of action and are impacting the disease state the same way. So it's difficult, it really is.

But I agree with you. Our Act is basically specific, and I think we've had to moderate a little bit on some disease states because it's very, very difficult to put patients into that setting scientifically and ethically.

RT: In some of the other countries, do they have the concerns or the legal constraints on experimentation with drugs that we try to enforce?

JES: It's funny that you mentioned that, because in the United States, the controls, studies, the trials were always controlled under Investigational New Drug submissions. As of May of this year, it's a requirement in Europe that they go through a CTA, a clinical trial application, where they look at investigational products. They're coming our way as we speak. I think it's fascinating. And it wouldn't have happened had it not been for harmonization. I think Europe saw the rigor and the logic of controlled clinical trials under the rubric of a regulatory agency.

We don't stop the research. That's not what we're here for. We get 150 new drug applications a year, but we get 20 times that number of investigational drugs, or more. I think last year we probably had maybe 1,200 investigational new drug applications. I mean, that's a lot of research that's going on. And all we ask is that we look at the protocols. We'll look at the drugs that are being administered so that we know that there are no overt safety issues. And I find that fascinating.

We're becoming more proactive and working much more closely with drug firms now than we ever did. I think that old friction has given way to a more cooperative effort. They're even talking about critical-path initiatives and streamlining the transition, so it's fascinating to be part of that.

RT: I think that's indicative in part of the leadership of the agency more to a science approach rather than strictly an oversight and regulatory one.

JES: That's right, a compliance approach. That's right; I agree. I think it's wonderful because I was in that boat. I was in academia trying to do that. And, you know, at some

point it becomes cumbersome sometimes to do research because of the requirements, and I think there has to be give, has to be a little bit of flexibility there if you think about it logically, and I think we're doing that. We may not be there for every drug candidate, but we're getting better.

As I work with some of these small firms that come to me for help now, I find it refreshing to hear the rather open discussion with our clinical divisions and all the disciplines, you know, and they get around the table like this and discuss how to resolve the problem that the company is struggling with rather than, if you don't do this, it's not going to get approved. That's a leap of faith that we've taken, and I think it's good.

RT: Well, we're speaking of the drug arena, but even in the food regulation, it was the same thing.

Back when I was in the field at the state level and worked with FDA people, you might see something that . . .

#### TAPE 1, SIDE B

RT: As we changed the tape, I was just suggesting that, recalling in earlier days, working with FDA field personnel, you might see something in the production area that is obvious, and if you tell the man -- and often they really wanted to be told -- the FDA people were reluctant to do that because some promotions were predicated on how many regulatory actions you developed. That was not conducive, really, to forward movement.



JES: I agree with that.

You know, I always tell stories when I speak publicly about, when's the last time anyone in the audience had been pulled over by a police officer and told they did a nice job on that left turn. It doesn't happen. The police officer will pull you over if you violate the law, but not if you obey it properly. And sometimes we have a tendency to do that here. It's unfortunate.

RT: Well, probably through the history of regulatory work of the agency, this one and others, through the years, there's a greater awareness of the advantages of cooperation. There may still be mavericks out there, but perhaps fewer in number than they once were.

JES: It's interesting. That's right.

JS: You made a reference earlier to a sort of cooperative relationship between FDA and USP, and I wondered if you could speak to that in terms of your own experiences doing research here and how that might have interacted with what USP's interests were.

JES: The perfect example was a project that we were involved in involving conjugated estrogens, a very difficult product. It's really a legacy product. It's been around for a long time. They basically harvest these conjugated estrogenic metabolites out of pregnant horse urine, and they market it as an extract. So, depending on the time that they harvest this and how many horses are involved, there's variability in the product,

plus there's many, many components: glycosylated estrogens, sulfated estrogens, all kinds of components in there.

We were looking at methods to look at the dissolution, disintegration, and quantitate each one of those. The USP didn't have a monograph chapter on this yet because of the difficulty, so we were working fairly closely with them, sharing the information with them that we could glean from working with some of the different formulations. We had U.S. formulation, European formulation, Canadian formulation. We had some drug standards, but a standard for a product that has wide variability is difficult, so it was a perfect kind of cross-fertilization research that was going on. And there are now monograph chapters in the USP that cover conjugated estrogens, and that was largely because of some of the work that we did, and I'm proud of that.

That was exciting and it was also difficult. It was not easy research. The methodology had to be developed. Companies were naturally suspicious of what we were trying to do, so we kind of had to pry information and standards and samples from them. It was quite an effort.

JS: Did you ever run across people, either within the agency or outside of the agency, shall we say, who were calling into question the agency's role in doing research as a recognized function and mission of the agency?

JES: That's right, there was -- I think you hit a nail squarely on the head. The question was, why are you doing research that firms should be doing, and my answer to that was that there are some types of research that really had to be done after that product has been

on the market and has matured, and the firm has absolutely no economic incentive to do that research. *We* need to understand the product, not the firm, because we're dealing now with issues of multi-sourcing and generic equivalency, and that's something that we (FDA) have to understand. We couldn't delegate that to a half-dozen different companies. It really had to be done here at the agency centrally along with people at the USP. And I think you could probably point to many, many types of research that are done like that at the agency that cut across disciplinary lines, cut across product lines. They're really looking more at the whole problem, not at a single product problem. So, where a firm will do research to develop their product, to understand their product, they don't necessarily do research to understand all the other products that are out there competing, and that's the type of research that I think is necessary.

RT: Did the adverse-drug-reaction program add any impetus to this, or was that primarily back to the manufacturer?

JES: I think no question. I think there are adverse reactions that are common, and the real commonality is in the formulation or the rate of delivery of the drug, not necessarily the purified drug itself or its action, but, rather, the input rate. I'll give you an example.

Many neurologic products are very lipophilic so they can cross the blood-brain barrier. I'll pick one. Let's say Valium. Valium immediate-release tablets are very low dose and persist in the body for a long period of time. I think the Valium half-life is probably somewhere around 70 hours plus. Now, that's for an immediate-release tablet. There are some controlled-release medications that don't have half-lives that long. So

you have to understand the science and the definitions and terminology. But for neurologic products, products that are very lipophilic, that cross the blood-brain barrier, they often persist in the body for very, very long periods of time. So we were looking at the logic or folly of defining a controlled-release product for that.

I remember talking with -- Valium, I think, is a Roche product -- the people at Roche, saying, "What are you trying to develop a controlled-release product for this for? This has got a half-life that's almost three days. I mean, what do you want this to do, to be delivered in the body over a week or longer?" It didn't make any sense scientifically. But that's the type of issue that I think we have to understand, and we have to be able to do some of that research here so that we can make those scientific judgments.

JS: Well, then, I have to ask, did they develop a controlled-release formulation?

JES: Never did, they never did. It was a nice way to extend their product, but, really, it was kind of newspeak.

JS: And just to follow up, the type of research that you're talking about that FDA would be very interested in but companies wouldn't, why wouldn't academic scientists be interested in this kind of research?

JES: I was always fascinated why they weren't. And I think it probably has changed with time. I'll give you a perfect example.

We've got former Center director Carl Peck with a research group at Georgetown looking at some of these things, Ray Woosley down in Arizona looking at the same thing. So I think academicians are finding that it is fascinating. Tufts' Center for Drug Study. It's fascinating to see academicians getting involved with some of the seminal questions that we have to deal with here, and I've found it fascinating to see it develop.

You know, when I was in the Office of Generic Drugs, I monitored a huge contract that we had involving research and training. We had the School of Pharmacy at the University of Maryland doing some of the research there, answering some of the questions that helped us formulate the SUPAC [Scale Up and Post Approval Changes], the initial post-approval changes guidances, and I find that fascinating, that we helped to pick out together with the university some signal drugs to look at. They could look at different formulations, and they would actually formulate some of those drugs over a wide spectrum of formulation parameters and see how rugged that drug formulation was. And we could pick out what things were critical and what things weren't to that formulation, so that when we were trying to formulate a guidance for industry, when they wanted to make post-approval changes, we used some of that research to help us simplify that guidance. So it can be done; academia can get involved, they have; and I think it's great, because oftentimes they can do more research than we can. We've got a fixed number of researchers, a fixed number of laboratories, and I think the academicians can really augment that.

RT: Presumably, some of those academicians may have students do a lot of the work.

JES: Exactly. These are great projects for students. I mean, I would have loved to have had something like that for my graduate students. But I think it's great.

JS: I want to return to getting you into the agency, although we sure can keep up discussions like this as we go along.

But when you came in in 1984, you were with the Division of Biopharmaceutics in the Office of Drug Standards, as you mentioned. Then you moved for five years to the Division of Cardio-Renal Drug Products. And what -- I wanted to see if you could characterize . . . I assume you were involved in evaluation of new drug applications. If you can tell us a little bit about that, how, both from your own perspective and what the process involved, among other scientists and physicians in that office, just to give us a sense of how a drug is evaluated in FDA from a scientist's perspective.

JES: That was one of the reasons that I moved to that clinical division. Back then, there was one Office of Drug Evaluation, and I think we had five, maybe six clinical divisions. Cardio-Renal was the biggest. It had cardio-renal drug products, the hementics, the GI products, a few other things. And Ray Lipicky came from academia, from the University of Cincinnati, so he was an academician at heart. And at that time, of all of the disciplines -- medical, pharm-tox, chemistry, statistics -- were all housed under a clinical division director. Today, it's slightly different. We've taken those disciplines and kind of pulled them out of clinical divisions, and I'll talk about that later. But originally, all of the disciplines reported to the clinical division director, who was the king of all he surveyed. And Ray was, I thought, a great guy because he had come from

the academic setting. He had done clinical research, so he knew some of the problems; he understood some of the problems. He allowed me to continue doing some of my research even as I was reviewing drugs in Cardio-Renal.

The one nice thing about being in a clinical division then was that whenever we were looking at a drug -- it doesn't matter if you call it drug XYZ -- we'd get around the table like this, just as we're sitting, and there would be a medical officer, a toxicologist, someone like me whose background is in formulation chemistry, and we would try to talk about issues that would impact the other, and you don't get that anywhere else. You really don't. That's the only place you can get it.

When I was in the Biopharmaceutics Division, we were a consult division. I never got that intimate interaction that I got when I was at the Division of Cardio-Renal Drug Products. And I'll give you an example.

One time, one of the clinicians, Bob Fenischel, who went on to become his deputy, I think, was looking at some clinical-trial results where, in the control placebo group, there was a higher dropout rate than in the treated group. And we were sitting there talking about it, and I said, "Bob, let me take a look at the formulations." And I took a look at the formulations and, lo and behold -- this was a high-dose drug, it was about a 600 mg. dose of active ingredient, but the finished tablet was probably about three-quarters of a gram; it was big. Well, in the placebo control group, they took the active ingredient out of the formulation, and in its place they put lactose. Most adults, at that age in their lives where they're having problems with their heart, are lactose intolerant, so taking the placebo, which was a high slug of lactose, was making them sick,

and they were dropping out of the study. They said, “No, don’t want any more of this!” And we solved that problem.

We got back in touch with the firm and said, “Look, I think you need to reformulate the placebo.” They did, and they went back in.

JS: [laughing] I’m sorry, it just sounds interesting to reformulate your placebos. I mean, was lactose a common ingredient in placebos?

JES: Absolutely. It’s cheap and it’s effective. It’s a byproduct from milk.

RT: Let me just add that, you said Bob. What was the last name?

JES: Fenischel, F-e-n-i-s-c-h-e-l, I believe. Bright guy, M.D.-Ph.D. And his Ph.D. was in computer sciences. And I forget where he joined us from. I think it might have been Arizona.

But there’s a case where it took two people sitting side by side talking about this to come up with a solution, and it wouldn’t have dawned on him. He was just looking at the numbers and seeing this high dropout rate, and was perplexed. And it took me maybe half a day and I’m looking at it, and all of a sudden I went, “Oh, my God, no wonder. This is a huge slug of lactose, and they’re getting it three times a day. They’re probably running to the toilet after the second dose with cramps and gas and all kinds of stuff. I don’t blame them. I would have dropped out too.”



JS: It's a new approach.

JES: But that's the type of thing that you have to look at, and it really has to be a multidisciplinary approach; or someone that's going to look at it holistically like that. But that's a funny story.

JS: So it sounds like this is very much a team approach.

JES: It has to be, absolutely has to be.

For instance, when I'm looking and my people are looking at the drug substance, just the purified drug substance, every new drug substance comes along with a list of impurities, and the Act doesn't deal with that. The Act just says that you shall not market a violative product. Well, what's that mean? You have to look at the science. If the drug substance is 95 percent pure and 5 percent of them are impurities, what are the impurities, and are any of those impurities toxic? Well, there's where you have to sit down with the toxicologists and say, "Can you help me with this? I'm measuring these levels at a percent, and at that level and at that dose, is this going to be a problem?" So we have to work together to come up with the appropriate standard for that. I can measure it, I can analyze it, I can look at it, I can define the structure and characterize it, but I need someone to help me determine whether or not it's toxic.

JS: Since you're talking about standards, could you walk us through where you go from FDA making decisions to the time that USP gets involved in it?

JES: Good point. Most of the standards development is done in that investigational stage.

You know, a company really goes through several phases as they're developing a product. They discover the product, and we don't even know about it yet. They discover this active and, you know, and eureka, somebody runs down the hall. They've got something that's active; it's a sedative. Okay? They do an awful lot of animal research and they do an awful lot of formulation research and they do an awful lot of manufacturing research before they even come to the agency, because when they come to the agency, they have to have a pretty idea of what they're giving people. It has to be formulated, it has to have pure substances in it, you have to know how many people you're going to give it to and what to look for.

When they start that process, that's when we get involved in looking at the standards. As it goes through early stages of clinical study to the middle stages of clinical studies, then on to the pivotal clinical trials, the company and the agency are refining product standards as we go, so that when the NDA is submitted, there are no questions about what impurities are toxic and how they're controlling those impurities. That's already been done. All we're doing now is agreeing that these are the official regulatory standards.

Now, after that product is approved and goes on the market -- the drug substance has those standards and the drug product has those standards -- the company can change their manufacturing, maybe look for different clinical indications, maybe even market it in different strengths or different presentations. That's part of the post-approval process.

Somewhere between that NDA approval and those post-approval changes, the USP gets involved. The firm will go to the USP and say, “We have a standard, a set of standards. We’d like you to make it an official compendial standard.” They take that body of information, publish it, much like the agency does, publish it in a pharmacopeal form, open it for comments, let people look at it -- academicians, other industry members, nonprofit institutions -- and they wait for comments to come back. And if the comments are valid, then they’ll adjust this final set of standards. Once it’s finalized, it goes into the USP as part of a compendia, and now anyone can buy it off the shelf.

I’m sure you’ve seen the USP. It’s about 2,500 pages. It looks like an old Bible. It’s got paper -- you can read both sides of it if you hold it up to the light. That’s how thin it is. And each chapter is usually two to three or four pages but really encompasses all of the standards that were developed in the clinical development, in the post-approval product development. And then it’s there for everyone in the world to look at and use, so that now if you pick up lovastatin off the shelf, you can go to the compendia, you can open it up to that chapter and say, “Oh, okay, this is how we characterize this product; this is how we characterize this drug substance.”

So those standards have had industry work, agency-industry cooperation, post-approval changes, and, finally, the compendia, because the compendia is the final chapter. Once that product has run its course and lost its patent, then that compendial standard becomes the standard for all the generic competitors. It’s that simple. And then, that’s the genesis of multisource standards. They all look to the USP, the compendial standards, for their characterization of drug substance and drug quality.

JS: So the compendial standard, then, is derived almost concomitant with marketing, not pre-marketing. Is that correct?

JES: That's right. I don't think I've ever seen a case where someone has submitted something to the compendium before they've gotten a product approved. Up to that point, it's really proprietary information.

If you look at any drug label, there are critical things in there. It has to list all of the excipients that are there, all the colorants that are there, because there are people that may be allergic to those things. What it doesn't do is give you the details of how much of each and how it's manufactured, how it's formulated, how it's put together.

So it's the result of all of that developmental work, but it doesn't give you any of the details of how we got there. And that's why we work cooperatively with the USP, because we know how that product matured and we know that if the compendia differs dramatically, that we ask questions: There seems to be a disconnect between the standards you have in your NDA and the standards you're proposing in the compendial chapter. So that's our role. We always took it fairly seriously.

That was part of the role of the manufacturing reviewer that oftentimes was off the books, if you had worked with a product from its genesis through to its approval, and then you got the compendial chapter, to look at it and review, you did that out of dedication to the commitment to make public standards meaningful, and that wasn't our primary review function. It was people like Charlotte Brunner and her colleagues who were very intimately involved in verifying those standards and things like that. So it was, it's an interesting effort.

There are a lot of people who work behind the scenes doing things like that who get very little thanks for it, but that the world and the public benefits, because I think the USP is probably the premier compendial set of standards.

JS: Are agency scientists like yourself actively involved in USP, in committees and so on?

JES: Absolutely, absolutely.

JS: What are some of the committees?

JES: I have people that were on specific committees for the types of products, or general committees like dissolution. How do you characterize the dissolution of a drug when it's a tablet, a capsule, a transdermal patch, a suspension? How do you do that? How does one design a test to fit all those situations? So I've had people that are involved in all of that, and I've personally been involved in some of that, and it's a cooperative effort. It's one of the challenges of the proposal and verification process. It's fascinating to see that evolve. And some issues never come to agreement.

Premarin, I'll talk about Premarin. That really languished for years because there were arguments over specificity and sensitivity and the ability to identify each component and what the meaning of that component was, and whether those components were in every single tablet. That was a huge back-and-forth discussion. It finally got settled, but after years and years of work.

JS: Returning back to your work in the Division of Cardio-Renal Products, you gave a wonderful, succinct summary of how things work when you evaluate a product and this approach. Are there particular approvals that stand out during your tenure there that you think are worth noting?

JES: Yes. I guess I have two comments on that.

One was, I was particularly proud of some of the work that we did on nitroglycerin. Nitroglycerin was an old drug, predated the agency, predated the agency by a good 50 years. The agency is celebrating its centennial; the USP is celebrating probably about 150 years of existence; and nitroglycerin had probably been around causing headaches in armaments factories for I don't know how much time prior to that. But it does have an effect. It's got a very good pharmacologic effect. It's used for angina, and people have been carrying around little bottles of these tiny little nitroglycerin tablets and putting them under the tongue for a long time.

Anyway, companies tried to develop other oral formulations, transdermal formulations, topical formulations, and I was involved in that -- not only in the review, but in the research. I'll give you an example.

Nitroglycerin, when it's put under the tongue as a sublingual tablet, dissolves and gets absorbed readily in the buccal cavity, part of the mouth. When you take it formulated as an oral pill, when you swallow it, it goes into the stomach and it's absorbed rather rapidly. The difference is, the first path of any drug after it's absorbed from the stomach is the liver, and the liver is a metabolizing machine. It tries every which way to

break things down into components that can be excreted. So nitroglycerin was being absorbed, going right to the liver, and the liver was killing it. We did work, animal studies and method development, that showed that, clearly, when controlled-release nitroglycerin was swallowed, we found very little, if any, in the bloodstream.

Now, contrast that with patch technology. There we saw blood levels. If you put nitroglycerin on the skin, it will absorb through the skin into the systemic circulation at high enough levels to be measured, and it exerts its pharmacologic effect.

RT: What would be the adverse effect of an excessive level in the bloodstream?

JES: A couple of things. First of all, you generally get dizzy and pass out, because if you relax the blood vessels too quickly, you suffer postural hypotension. You drop like a mass on the floor. And anybody that's tall, like I am, suffers that anyway. When I stand up quickly, I'll get lightheaded, especially when I'm close to her. At any rate, so excessive levels are bad.

Nitroglycerin is really a short-acting, quick-acting agent that is meant to get to the heart, relax the blood vessels around the heart, and then be done with it, be excreted. So when we started looking at these different dosage forms, which were being developed under the DESI [Drug Efficacy Study Implementation] laws, we found that we were kind of from Missouri. We were saying, "Show me and prove it to me."

JS: But just one more thing. What was the problem with sublingual administration of nitroglycerin?

JES: Here's the problem. Nitroglycerin has a fairly finite evaporation rate. If you were to take a nitroglycerin sublingual tablet, sit it out on the table and leave it there, in a matter of a few days it wouldn't have much nitroglycerin left in it because it evaporates. It's formulated in what's called an adsorbate. They adsorb it onto something and then they formulate it into a tiny tablet, and they extrude the tablet, dry it, and it gets put in a little . . . You'll see people that carry them, will carry them in a little tightly sealed container; it's got a little O-ring on it so that the nitroglycerin doesn't evaporate at high rates. So it's very effective, but its shelf life is lousy. So they were trying to come up with other ways to deliver it.

The patch has turned out not a bad way to do it. If we deliver it over a period of time, you can put it on your chest or your arm, and it was very effective.

But the oral tablets, you know, we kind of shot that like a fish in a barrel, and it really died a natural death. None of those products remained on the market.

And it was nice to be part of the evaluation as well as the research. It made a tremendous impact when you sat down with the company at a meeting and said, "You know, we did some research here. I'm not getting the same data that you show. Explain to me why."

Their eyes got big as saucers. "What do you mean? How much do you know about this?"

"Well, we've done some animal studies and we've looked at these formulations, and we don't see measurable amounts in the blood."

How do you refute that?



It makes a great impact when your own scientists know something about what they're talking about and have some hands-on experience. So I always felt that that was valuable, and I enjoyed that. It wasn't a matter of one-upmanship or leverage; it was simply, I'm calling it as I see it, show your data and I'll show you mine, and let's see if we can come to an agreement.

Some of those products are on the market. There's still sublingual nitroglycerin, there's still patches on the market, but the oral tablets are gone.

JS: So we had oral tablets.

JES: Yes.

JS: Between '38 and '60, maybe before '38. But with the DESI study, that effectively did away with that.

JES: That's right, and that was nice.

JS: If they were not effective, why were they still on the market?

#### TAPE 2, SIDE A

JES: So, to pick up where we left off, there were a lot of products. These drug-efficacy studies or DESI studies really pertained to the products that were approved after the '38

safety amendments but prior to the '62 efficacy amendments. And the DESI studies were really a mandate. You'd see all the announcements in the *Federal Register*. We would like companies that market these products to come back and show us efficacy.

The whole purpose was so that we could come up with labeling.

You know, all products are approved for an indication, and that indication should be clearly put on the label so that clinicians and health practitioners know what that drug is for. And it should also document the contraindications and side effects and/or maybe even the problems of overdosing. All of that belongs in the labeling. And the DESI studies -- I mentioned there were a large number of them because many of those products are still on the market today as we speak. Nitroglycerin is still being used by millions of people.

When it was first put on the market, there were no efficacy studies requirements. Studies were done during the period that mandated the DESI, and that was a long, dynamic process. There were studies that went back and forth.

Some of them were class studies where groups of companies would do . . . On the nitroglycerin studies, there were multi-company studies under Ray Lipicky. He wanted to see cooperation between the people who were marketing these products so that the labeling could in fact honestly and openly delineate how much to dose, what for, what period of time, were there any untoward effects, and the labeling is now in pretty decent shape; but it was because of the efforts of those like Ray Lipicky working with the drug company to come up with honest, reliable labeling for those products.

Just because it was approved in '38 doesn't necessarily mean it was terribly efficacious because that wasn't a requirement then. Those '38 amendments were done in

response to poisonings, the sulfanilamide episodes. And the '62 amendments were really in response to the thalidomide problems.

So, much like any regulatory agency, there's an evolutionary process. That FD&C Act has been amended 100 times since it first got passed in 1906. And usually it's in response to something that happened that was untoward: poisonings, toxicities, mutagenicities, carcinogenicities. There are very few parts of the Act that are really forward-thinking.

I like to explain to people that I think one of the most forward-thinking acts that came out of Congress with respect to drugs was the Waxman and Hatch Act. That was quite a compromise between the big-pharma companies and the small generic firms. Since that time -- and I was part of that evolutionary process -- generic products no longer have to have efficacy studies or toxicity studies associated with them. That's already been done. Now it's a matter of bioequivalence, pharmaceutical equivalence, and manufacturing reproducibility. And that Act really has made that process easier, more streamlined, faster. We now have cheaper generic products on the market for grandma and grandpa. So sometimes Congress does some good things, you know.

JS: You might say the orphan drugs.

JES: Orphan drugs, same thing. Yes, absolutely. It was needed, and what was done was appropriate. The Act and the changes to the Act allowed us to do that, allowed us to identify those drugs and help bring them along faster.

JS: You mentioned nitroglycerin as one. I thought I might have heard you say there was something else that maybe stood out during those Cardio-Renal days. The nitroglycerin story is certainly a wonderful one.

JES: Well, there are others too. I remember getting involved in -- it's interesting.

Isoniazid was used for years to treat TB, and its use had kind of come and peaked and waned as TB dropped off. But the AIDS population kept that door open, and we found the disease making a comeback in prisons and other places; tuberculosis was an adventitious disease. It took advantage of the condition, so we had TB rearing its ugly head again.

Well, Isoniazid had come and gone. It was the therapy of the day, and then as TB dropped off, its use dropped off and its manufacturing dropped off.

One of the things that we'd never looked at, because Isoniazid was another one of those old agents; it was on the market back in the '30s and '40s . . .

JS: Streptomycins.

JES: That's right, exactly.

One of the problems with it is that, in the body, it breaks down to generate hydrazine. Hydrazine is rocket fuel. It's nasty stuff. When I handle pure hydrazine, I put on gloves and a mask and work in a hood. This is nasty stuff. But it's a natural breakdown product of that drug.

We got involved evaluating it. I published some papers on it because companies were formulating it in other than oral tablets. They were looking at liquids and things like that, and we were finding very high levels of hydrazine in the products.

Now, this isn't really an efficacy problem. It's a safety problem. And it required that the FDA be able to delineate what was happening. Do you go back and make the innovator firm do this research, or do we do some of it ourselves? Well, we did some of it ourselves and we came up with some interesting work, I think. And I think it helped us deal with some of the generic firms that were trying to manufacture other than tablet formulations for this product.

For some people, when they're sick enough, taking a tablet is difficult. They can't swallow properly or they can't sit up. So an oral liquid is an appropriate way to dose them. And if in the oral liquid formulation, it accelerated the breakdown of the parent drug, something had to be done to change that formulation so that it didn't do that, and we got involved in that. That was fascinating. We really resolved the problem. We did some work, we presented it, shared it with firms, shared it with the Office of Generic Drugs, and it was very well received.

Two examples.

JS: Excellent.

You mentioned generic drugs, and you moved to the Office of Generic Drugs in 1991, where you were for five years, until 1996. And we wonder, of course, what impact of the generic-drug scandal of the very late 1980s -- did you still witness when you were there?

JES: Well, it's interesting. Let me go back to when I was in the Cardio-Renal Division.

My office was on the 16<sup>th</sup> floor in the Parklawn Building. The Office of Generic Drugs was on the 17<sup>th</sup> floor; Marvin Seife's group was up on 17. And don't pin me down to what the year was. I think it was '89 when we heard thumping and bumping upstairs as armed guards came in and padlocked offices. People like Charlie Chang it turns out had been very intimate with some generic-drug representatives, had accepted gifts. It was a real embarrassment for us. I don't think . . .

You know, one of the problems with a career in a regulatory agency is you have to live with the successes and you also have to live with the embarrassments, and that was an embarrassment that we all felt.

Well, they brought in Roger Williams from the West Coast. He was at the University of San Francisco. And he took the Division of Generic Drugs from a division to an Office. We threw lots of resources at it. And I was recruited to join the Office to form a recruitment and training branch, which is what I did.

JS: Was it difficult for you to step into an office like that just after what had happened?

JES: Yes, it was, for a couple of reasons. First of all, here I had been in New Drugs my entire career here. I was an outsider. I was coming in from outside the group, in a high-level visible position to do something that really people within the then-Division of

Generic Drugs felt that maybe someone within that group should get that opportunity, be promoted to do a job of recruitment and training. So I came in from the outside not having had any hands-on experience in generic drugs, and I brought with me my career, up to that point, in New Drugs.

So I worked very closely with Bob Jerussi and Roger Williams and Doug Sporn, his deputy. We embarked on a program of intense recruitment and training. Everyone in that expanded review cadre, whether they were chemists or biopharmaceuticists or project managers, all spent some time with me and my team in a formal program talking about the review process, talking about the law, talking about what our responsibilities and roles should be, talking about how to work together. Every new employee in the Office of Generic Drugs spent some time with me and my team, and it was fascinating.

I had to write a report on a quarterly basis and meet with the representatives from Congressman [Henry] Waxman's staff. It was a guy that used to come in with a bowtie and one of his senior staffers, and they'd sit down and talk about, how's the recruitment going, how are the changes going, what is the level of training, because one of the things that came out of the Kibbey report was that the Office of Generic Drugs personnel really didn't have a lot of formal training. So this was really the genesis for more rigorous training. And since I'd come from academia, it was something that I enjoyed doing anyway, so I basically wrote the curriculum and wrote up examples and case studies and took people from day one -- I know nothing about a regulatory agency -- to a functional reviewer, and it was really a labor of love. I enjoyed it.

And after the recruitment waned and we became more established, at that time we had a couple of chemistry divisions and a biopharmaceutics division and a team of

labeling reviewers, once we matured to that point, then I took over the normal review of the group and I did training as needed.

RT: Were these recruits from elsewhere in the agency or from the outside?

JES: Outside completely. We wanted these folks to have absolutely no exposure and experience other than industrial or academic. So we went on just a rampage. We went to national meetings, we went to magazines, advertising, journals, technical journals that would target people, and it just -- the hiring went on for the better part of two and a half years.

RT: Was it difficult to interest people in FDA employment?

JES: It was, it was, because in industry, they were already making pretty good salaries and they got stocks and year-end bonuses, and we couldn't promise them much other than a government position and a pension.

RT: And then they'd have to divest themselves of some of their investments.

JES: Exactly, sometimes not happily, sometimes at a loss. If you joined us from Bristol Myers Squibb and Bristol Myers Squibb stock was selling at \$65 a share when you left and you divested it and it dropped down to \$61, guess what? You ate the loss.



And that's one of the problems with recruiting people to the agency, is that we have to be squeaky-clean. There can be no appearance of conflict. It's very difficult.

So you really do have to attract people that are looking for something different or they're at a point in their career where they want to try something, much like I did, and are willing to make that transition and learn what they need to about the law so that they can apply the science they need to, and it was a real challenge. I enjoyed it.

As a matter of fact, we did something that I'm very proud of. I talked about this interaction at the University of Maryland and the inception of post-approval change guidance. We put out the very first SUPAC, which stood for Scale-Up and Post-Approval Change guidance, and we tried to delineate four or five areas in which a company could vary their product and minimize the amount of information that they submitted to the agency for approval.

After we wrote the guidance, myself, in conjunction with some representatives from industry, we had a representative from New Drugs, who at the time was Chi Wan Chen, a representative from OGD, who was me, and then about a half-dozen industry volunteers actually worked up an internal-external training program to launch this. We went over to a UHF station facilities over in Virginia and videotaped vignettes of examples of case studies.

I have a set of four master tapes at home -- if you want, I can share them with you -- in which we've got FDA representatives, myself included, on tape talking about issues regarding post-approval changes.

JS: What time period are we talking? When was this done?

JES: Nineteen ninety -- it's probably not in there -- probably around '94, '95.

JS: Mid-'90s.

JES: Mid-'90s. And the group of us got a commissioner's-level award, which I'm very proud of.

JS: Was this the origin of this SUPAC?

JES: Yes, yes, and it was really neat.

So we had a guidance and we had training for both internal consumption and external consumption. And I remember when we had the external meeting, there must have been about 400 people who showed up, and someone would give a short talk, and then they played one of these videotaped sessions. And one of the sessions that I was in generated laughter throughout the audience because I had to say over the phone to someone, "I'm sorry, that change really doesn't qualify. You can't do that." And the audience burst out laughing because it just, you know, it kind of personified to the audience how the agency sometimes suppressed change. And it was interesting.

JS: So, what happened to SUPAC?

JES: SUPAC took on a life of its own. If you look at our website now, there must be eight or 10 post-approval-change guidances, scale-up, semi-solids, some of the ones that I've worked on, but I'm drawing a blank, injectable products, modified controlled-release products -- that was one I worked on. And companies can now go to the website, download this guidance of anywhere from 15 to 30 pages which is replete with best advice of the time plus some examples, case studies, and they no longer have to pick up the phone and talk to someone or come in to meet before they do make a submission to the agency. They now have information that gives them some history. And I was very proud of that.

That was, I think, a great accomplishment at the time, because up to that point, we only had the Act and the CFR's [Code of Federal Regulations], the federal regulations. We really didn't have a lot of information that was background in nature for people to read so that they knew what we were talking about, so they understood when we say a post-approval change, what do we mean; this is what we mean. If you make this type of change, this is what we expect you to submit. And I think that really helped streamline the process and then really helped to foster the cooperative attitude. What I think it really did was it broke the logjam of trust and communication between industry and the agency.

In order for industry to agree to these guidelines, they have to be part of the discussion and part of the genesis, and I think that's important. We could pass a law or write a regulation that says, with the submission of a post-approval change, we want the firstborn of the executive vice president. That's not reasonable. But what's reasonable is you report the change, you report its impact on stability, you report its impact on bioavailability, and that's sufficient. And I think that requires not only the regulator

writing that up, but also someone out there in the real world saying, “We can do that,” or “We disagree, we can’t quite do that; we can do this.”

So I think that’s really been the genesis of some of the discussion that I think now is commonplace -- ICM, ICH, and other venues like that.

RT: Earlier in the process of things, there was quite a bit of congressional oversight on the so-called drug lag. Were you involved in any of those hearings and discussions?

JES: I haven’t been involved in the hearings, but I have been involved in some of the responses that the agency took to address those issues, like the critical path, like process analytical technology, that have come out of the woodwork as potential solutions to the drug lag.

PDUFA [Prescription Drug User Fee Act]. The first PDUFA was written at a pretty high level. We’re into our third renewal now. It’s been almost 15 years since we’ve been taking . . . You know, now when an application comes in, it comes in with a check. The check is not unsubstantial. It’s about three-quarters of a million dollars.

PDUFA II and PDUFA III, I was very intimate in coming up with proposals to put into those for Congress to pass, and I think some of them have been valuable. We talked about streamlining the post-approval process, and that was part of PDUFA’s impact on new drugs. We talked about what could we charge for and what couldn’t we charge for.

One of the things that I think you’ll probably see raise its head in PDUFA IV, which they’re negotiating now, are some of the suggestions that came out of our office.

When a company comes in to meet with us, they submit a meeting package with a proposal that they'd like to air with the agency representatives, the appropriate people. We receive the package. It's not really an official submission. It's not an amendment, it's not a supplement, it's not an NDA [New Drug Application], it's not an IND [Investigational New Drug]. It's a proposal. We have to read it, comment on it, and be prepared to talk intelligently when the meeting comes up.

JS: Give us an example. What might this be? It doesn't have to be a specific thing.

JES: I'll give you a primary example.

For anyone that wants to start an investigational drug, before they come in with an IND submission, which really locks them in -- it's a written document; it says this is what we're going to administer, this is where it comes from, this is how many people it's going into, this is what we're going to monitor -- before it comes in, companies will often meet with us in a pre-IND meeting. And what they'll say is, "Look, this is the study that we've proposed to do. This is the drug as we understand it. How does that sound to you?" They'd like to bounce it off of us before they come in, because once they submit it as an IND, we've got 30 days to say you can proceed or not. If there's a problem, don't proceed. They'd like to get all that settled beforehand.

So, most companies that are intelligent come in for a pre-IND meeting. But we don't charge any PDUFA money for that. But it takes up 20, 30, 40 man-hours to prepare for the meeting, to sit and talk with the company, to write answers to their questions, to discuss intelligently some of the issues. And then we do post-approval minutes, a

compilation of what we discussed. Who pays for that? That's all time that's off the books. It's not evaluating a new drug; it's not evaluating an investigational drug. It's all before it starts. So, should we be charging for some of that time? I think you'll see that come up in the next PDUFA cycle.

RT: Has that ever been, that need ever been expressed to people on the Hill?

JES: Absolutely. That's what happens, you know. The funny thing about regulatory agencies, as you know, we can't politic Congress, but Congress understands that they don't know all the details, and they really do depend on us to give them some ideas to act on.

RT: Probably the staff people serving the member.

JES: Exactly. So what we do is we do the rough draft: these are the ideas to vet. We can do this; we can accomplish this on a deadline. And then Congress has to look at it and kick it around, shorten it, lengthen it, throw it out the door for a vote. And when they do, that's what happens.

So we had -- and I was part of that -- we had an impact on PDUFA II, PDUFA III, certainly. PDUFA I was rather rudimentary in a lot of respects. PDUFA II and III really refined that whole process of timelines and goals and how many things had to be reviewed within a certain number of days. And we've got a fairly well-established system now that I think makes the system work better. It challenges us at the agency to

do what everybody in the world does. They set goal dates and they meet them. So we're doing that now too.

JS: Did you run across, either personally or in your office, many instances of PDUFA-related expenses in which industry said, "That's not a PDUFA-related expense"?

JES: Yes, yes. The original PDUFA was really -- the Prescription Drug User Fee Act was meant to provide resources to review and evaluate new products.

Now, part of that evaluation has always been a field inspection. Industry said, "No, we don't want any parts of it. We're not going to pay for inspections. We don't mind paying for hiring additional people, giving them desks, putting computers on their desks, but we're not going to pay for inspections." So how do you meld those two? How do you reconcile them? Because, clearly, one of the things that every one of my reviewers used to do was, when they got a New Drug Application in, one of the first things they did was evaluate to see what facilities were involved, and then send an electronic message over to our Office of Compliance, and our Office of Compliance would initiate communication with the appropriate district office and say, "Would you please evaluate this facility for us." Part of the Prescription Drug User Fee Act mandates that those facilities be inspected and in good manufacturing compliance before the product is approved, so you can't separate those two. But industry didn't want to have any parts of paying for that, so that's always been a struggle. Can we use indirect expenses in some way or other?

It has been a significant profit center for the Center for Drugs and the Center for Biologics. If we get 150 new applications a year and each one is accompanied with a check, those checks add up through the year. At half-a-million dollars, 100 applications, \$50 million. It's a lot of money. It pays for salaries, it pays for physical plant, it pays for computers, it pays for technology, it pays for IT -- anything that you need to keep that system going. But they refuse to allow it to be used directly for inspection of facilities.

JS: The law says that explicitly.

JES: That's right. It's a problem.

JS: Certainly ORA would be involved in that. Right?

JES: That's a problem.

Now, I'll give you another example.

The Act stipulates that for a drug that's never been on the market before, that it come in under classification 505(a), which is a new drug, 505(j), which is a generic drug. How do we evaluate products that aren't 5(a)'s and they're not generic? There are companies that submit variations on the innovator product, maybe a different formulation, maybe a safety issue that's been resolved. Okay? We call those 505(b)(2)'s. Now, it's not really a PDUFA product. How do we evaluate those, and who pays for it? So those are the types of things where we utilize our new-drug review staff to evaluate those. We know good and well that those people are paid with PDUFA



dollars, but yet they're evaluating something that's not truly an innovative product. So those are things that happen all the time and we have to be pragmatic about them. You can't always subdivide people's time and attribute 20 percent of it to this, 20 percent of it to that. The person gets paid to do a job. It's the same job whether it's a 505(b)(1) or a 505(b)(2) or a 505(j) or a 507. Those are issues that we struggle with under PDUFA.

JS: You obviously alluded to this issue of creating elements of the agency that are pretty flush and other parts of the agency that aren't so flush, and I guess that creates problems too, doesn't it?

JES: I think the Office of Generic Drugs is struggling right now because they've never been included in PDUFA. We've always felt that in order to encourage generic drugs, there should be no fees involved with them, and that staff is funded by a line item in the budget. And if they need people because there's an influx of applications, they must justify increased staffing.

If we have a tragedy, you have to be able to respond to that tragedy, and it's hard to attribute where the dollar comes from to do that. I'll give you an example.

We had -- you probably remember a few years ago, there was a Kansas City pharmacist that had diluted some oncology products. He's now serving time in prison. But we had to not only discuss it with our field colleagues, but provide some of the methodology so that they could measure these things and evaluate what this guy was doing. So, is that PDUFA money? Is it appropriate?

[Recorder turned off for break]

RT: We're resuming now after a short break.

JS: And before we move on, I was just going to briefly ask you about that early period of yours in the Office of Generic Drugs when you were talking about developing a training framework for the employees. And you mentioned something about the very close involvement of staff of Representative Waxman. I wonder if you could just say a little bit about that, how that sort of connection unfolded, what it was like for you with a member of the Hill staff directly involved in what you were doing here in FDA pretty closely.

JES: It's interesting. You know, members of Congress can only be on top of so many things. Every congress person has a staff of people . . .

#### TAPE 2, SIDE B

JES: Each congressperson -- and I haven't interacted with many -- but each congressperson has got a staff that they delegate to do certain things. Each congressperson also generally presides over a subcommittee or a committee. Well, we dealt with Congressman Henry Waxman's staff. Waxman had a very deep personal interest in this, and the one staffer -- and I can't remember his name -- used to come in on a quarterly basis, and we'd talk about all the issues that they were concerned about:

sufficient staffing, training of that staff, the process that we follow, whether that process was adhered to and whether there was any deviations from that process.

One of the things that came out of the scandal was that applications weren't dealt with in a sequential way. If company XYZ came in with a generic equivalent and company ABC came in with a generic equivalent, sometimes the staff would take one of those and put it in a drawer and sit on it for a while and delay the approval of that application under the guise of efficiency or workflow. Now, Charlie Chang was famous for doing that, apparently. He would take a competitor's generic application and put it in a drawer, and it wouldn't get reviewed for a while. Well, that was considered favoritism.

So we went to the queue process in which an application came in and it got assigned a number in the queue, waiting to be looked at, and the only deviations allowed were under certain circumstances, such as public health or shortage or any number of things that might bring that out and expedite its review. But you had to define it, you had to justify it, and you had to document it. And congressional staffers wanted to know all the details. They wanted to know how many applications we processed, how many deviations from the queue, how many people were hired, where they were assigned, how long their training period was. All of this had to be documented. So I would write these quarterly reports. And sometimes the exchanges were very pleasant; sometimes they were heated; sometimes they would ask pointed questions: "What do you mean you didn't hire any new people this quarter. Why not? What was the problem?"

The federal hiring system itself was a problem. Oftentimes, bringing people into government is a very slow, laborious process. Unlike industry, if you're finishing up your degree, if I go to work for Pfizer, they'll say, "Look, you start tomorrow, and if you

need to go back to do something to defend your dissertation or whatever, we'll handle that." In government, you can't do that. If someone says they're working on their doctorate, they have to show you a piece of paper that says they got it, and from what university, and they have to have an attached list of coursework, because believe it or not, there are people that actually falsify their credentials, so we have to see whether they've done what they've claimed before we hire them, not afterwards. And that process is slow and painstaking. You have to do a background investigation; you have to look and see whether that person has accomplished what they say they have accomplished; and maybe you can make them an offer. And sometimes that process would be delayed up because of clerical support or any number of things that might delay the documentation of a candidate. And there would be pointed questions: "Why are you running under your staffing limits? Why haven't you staffed up? What are you not doing?" They wanted to know that. It sometimes got heated.

Sometimes one of our problems was one of an embarrassment of riches. By that I mean, when a product lost its patent protection, oftentimes three or four or 10 companies would come in with an application to get a generic approved. And the more applications that we could approve as quickly as possible, the lower the price became, because each company that got a generic product approved and on the market would undercut the preceding competitors by a few cents or a percentage. So the ultimate was that the cost of that drug would rush from two dollars a tablet down to fifty cents a tablet, then thirty-five cents a tablet, and ultimately become much more affordable. The goal was to get as many competitors on the market at the same time as possible, so we would try very hard to not give any one of those 10 competitors an advantage. And Congress wanted to know

the details. If Lipitor was going off patent, then we would like to know how many applications you're going to approve because we'd like to see the cost of that drop so the government isn't buying drugs for grandma at two dollars a tablet but rather at forty cents a tablet, and that was often a heated discussion.

RT: So as far as hearings are concerned, I suppose the Center director and/or Commissioner usually was the witness.

JES: Exactly. They would bring the appropriate reference people with them, because oftentimes they would have to concur, cover the mike and talk for a few minutes with someone that was knowledgeable so that they could answer.

RT: Did you sometimes have to take to the hearing rather voluminous records?

JES: Absolutely, absolutely.

I often wondered what happened to all that. Here we are, you know, how many years post-scandal. What happens to all that stuff? We wonder. I'm sure it's archived.

JS: We have a records schedule in the agency, and I can't tell you off the top of my head what . . .

JES: Are they trying to turn that into some sort of digital record so that . . .

JS: We can't take all of the paper that we've generated as an agency and scan that and digitize it. It's just not feasible. So you develop a record schedule that takes into account the significance of a record and you try to apply things across the board, so you use a rational process. So many things now are generated digitally, but you still have to have an assessment of the records and their significance.

JES: Because at that point, they were written reports and perishable. Somewhere in the bowels somewhere, those things are being archived.

JS: I trust they are.

I want to touch on three products in particular that you were involved in. I believe this was during your period that you were in the Office, as a manager in the Office of New Drug Chemistry from about 1996 to 2005. And the products I have in mind, first Gleevec, and Mylotarg, and the Cypher drug-eluting stent.

JES: Wonderful ones.

JS: Now, certainly not all drugs are announced with press conferences at the White House, with the President and the Secretary and the FDA Commissioner present, but this was the case with Gleevec. I wonder if you could talk about that, tell me how you were involved in this, and why this drug was important.

JES: Well, Gleevec -- up to that point, almost all anticancer agents were what I would call either strongly or moderately cytotoxic. They were cell killers. Cancer is a proliferative disease. Cells get out of control and they just multiply, and one way to suppress it is to kill them. So if you look at things like mustargen and Oncovin and all these things that are on the market, they're very toxic drugs. They're not easy to handle. They have to be handled with gloves and a hood. They have to be administered quickly. They vesiculate the vessels that they get injected into. The vessels will thin and collapse. Nasty stuff. Gleevec was a horse of a different color.

When Novartis first approached us on Gleevec, they said, "We've got something that we have evidence, clinical evidence that this stuff doesn't make people lose 50 pounds, their hair doesn't drop out. They just get better."

When we saw that develop during clinical development, we made the decision that this was going to be an expedited review process. So I had a team. When I was in the Woodmont Building with the Oncology Division, I had a team -- a supervisor and a half-dozen reviewers on that team. When we found out early on that this was going to be an expedited process and that it really was a breakthrough therapy, it was very different, its mechanism of action was very specific for the enzyme that was involved, kinase enzyme, we took the reviewer, cleared his desk, said, "This is your task." Now, we interacted with Novartis through the last stages of clinical development and into the early stages of NDA submission and we're going to work closely with them. Exchange questions before the NDA comes in, even during the investigational stages. You're going to exchange information with them. You'll meet frequently with them. I want you to go out on the inspection along with the investigator." There were facilities in Europe where

it was being manufactured. When this application hit the desk, they wanted it stamped as an NDA, an official NDA.

My reviewer concentrated on Gleevec, nothing else on his desk. We scheduled, even before the NDA came in, we scheduled a joint inspection with an investigator. We had that already in place. We dealt with our colleagues in Compliance in ORA so that our reviewer was briefing the investigator on this product by phone and by fax; he met this investigator in Germany, in Europe; went through the facilities together, the reviewer and the inspector; and iteratively discussed issues with the company right there. The company had their representatives, we had our reviewer there, we had an investigator there. Any issues that couldn't be resolved at that meeting right there at the facilities, we brought back with us and worked on iteratively by phone and fax.

JS: How early in the IND process were we involved in this?

JES: I'm trying to remember exactly when they deemed this to be an expedited-review process or fast-track process. I'm going to say it was probably in mid-Phase II. There's normally three phases to an investigation: preliminary, intermediate, and then pivotal clinical trials. Before it went to pivotal clinical trials, we had a hint that this was an interesting product.

So from that point on, those months of clinical trials plus the time leading up to the NDA submission, we were working closely with Novartis. It was truly a cooperative effort. Our reviewer, not only the CMC reviewer but the toxicology reviewer, medical officer, all were interactively working with Novartis staff at some level.



When they came in and got its date stamped on day zero, we were actually ready to approve this in about two months, eight weeks. We had to wait till the tenth week because they wanted to have, as you said, a big public pronouncement. They had Novartis there, Tommy Thompson was there, the Commissioner was there, our team was there. Novartis gave us a beautiful glass plaque with engraving on it thanking the agency, acknowledging the people that had worked on it, and it was truly a, I think, a model effort for what you could do for a breakthrough therapy, and it really, truly was.

People with these myelomas really don't have a lot of hope, and this stuff simply kept them well, and we saw recession and diminishment of the cancerous growths. They finally disappeared. I don't know how long this will be effective, probably until some genetic mutation takes place, but there are people that have had their lives prolonged infinitely because of this product. It doesn't work in all patients, it doesn't work for all cancers, but for this specific cancer, it's just marvelous.

There are now several other kinase-specific inhibitors on the market that are doing the same thing for other cancers.

RT: What kind of cancer is this?

JES: This was a myelolytic leukemia, and it was also effective against stromal tumors of the stomach. But it was a truly heroic effort, it really was. I was proud of it. I was very proud of our people for the way they did it. They did it very professionally.

You know, normally what we do with a typical NDA when it comes in, the reviewer will review the entire document, get together with the other team members,

they'll delineate in writing what the deficiencies are, send that letter to the company, the company will respond. We did all of this by phone and fax. I think there was no stone unturned to accelerate this process.

I don't think we can do this for every product. It would take a Herculean effort on our part. But for a truly breakthrough therapy for a disease state in which there is no resolution, this was marvelous. We did it for AIDS, we did it for cancer, we do it for some of the, as you said, orphan products for orphan disease states where there really is no hope for some of these people. What do you do for kids that have lead poisoning? That's a very select group of people. So we would do the same type of thing for them.

I thought it was, as I said, a model for the way the agency and the industry can cooperate to get things done, to move mountains, and I think we were acknowledged appropriately. It was something to praise the folks that were involved, to acknowledge that they've done a wonderful thing. And I just wish we could give cash awards and bonuses to people for things like this. I think it's a great way to let people know that you put your money where your mouth is.

Unfortunately in government, as you all well know, oftentimes doing a good job in government is a little like wetting yourself in a dark suit. You get a warm feeling but nobody notices.

JS: By the way, you said the reviewer's desk was cleared. Typically, what's the reviewer have on the desk at one time?

JES: Good question. It's not untypical for a reviewer at any given time to have a new drug application, maybe five investigational drug applications, and maybe another 15 post-approval-change supplements all on his or her desk at once. We moved all that out of the way so that this person could focus his energy. That meant someone else, in an unsung heroic way, picked up that slack. So it's awfully tough sometimes in government. There are people that are in the limelight and then there are people behind the scenes.

And as a manager, try to talk somebody into doing something like that when there's nothing in it for them, say, "Hey, look, this is what we'd like you to do. Can you do it? Are you willing to?" That's not an easy task as a manager in government because oftentimes people will just kind of push themselves away from the desk and say, "Look, I've got this much to do, only so much time. Can you get somebody else to do it?" And they're within their rights to do that. But every once in a while, I've always found that my staff in particular had a certain esprit de corps that just focused on that. And one of the ways I awarded people was to promote them.

We can promote people in the management ladder or we can promote people in the technical ladder, and nothing speaks like showing people that you support them. So I always, I think, tried my darnedest to identify people that did a good job like that, who might not be management material but certainly did the technical work supremely, and promote them, give them a raise, acknowledge that to people. And I think that builds an incredible loyalty.

RT: This program of management by objective, as a manager yourself of this kind of a staff, is that approach helpful or not helpful to getting accomplished what you've been speaking of?

JES: It can be. I think the problem is, when you identify something that requires additional effort, there's very few rewards in that system. We've become, with PDUFA, we've become victims of bean counting: how many things did you do? We rarely reward people for doing an excellent job on one thing. It's unfortunate. I wish I had a better solution. That's for another discussion.

RT: I've known someone in the field who once working on something else not specified in his work plan, and at evaluation time, the manager hadn't shown this change in the work plan.

JES: That's right, yes.

RT: Thus, because of no change in the criteria, the employee really suffered for having made the effort that was extra.

JES: That's right, absolutely. That is a problem.

JS: There's another product I want to talk about too. This was the first major combination product, Mylotarg, a combination of a monoclonal antibody and a cytotoxic

agent, and this was also a product that you were intimately involved in. Tell me about that development and what was involved.

JES: At the time, CBER was still a separate entity. All the therapeutic proteins came out of the Center for Biologics, and all the classical small molecules came out of the Center for Drugs, by and large. And we were trying to craft solutions to what happens when people put them together, how do we do that, because you need expertise from two centers to do this effectively. Mylotarg was, again, I think, really the first combination product that we had a trial run on. But the monoclonal was clearly a biological therapeutic protein, and calicheamycin was clearly a small classical cytotoxic agent. And we needed people from the Center for Biologics to review how the monoclonal was made, harvested, purified, stored, and then we needed our folks, in a joint fashion, to look at how we put that small molecule on the protein. You know, this small molecule is the edge of my thumbnail, and the rest of the protein is my hand. That's how tiny this thing is. It's just a tiny little molecule that's appended onto a huge protein that's folding back and forth, and it's made to recognize a certain type of tissue.

There were issues regarding the protein and its stability and its ability to remain active and specific for a target tissue even after it had been chemically modified and linked to a cytotoxic agent. So we had to have two groups of reviewers meet on a regular basis to discuss issues so that there wasn't anything missed. And then layered on top of that chemistry issue was the issue of the safety -- was it toxic -- and the efficacy -- did it concentrate in the tissue that we wanted it to, and did it have the effect that we wanted it to have -- very, very, very interdisciplinary, very, very cross-Center.

And I think the work that we did with Mylotarg set a pattern for how we were going to do combination products in the future, so that when the Cypher stent came along, we had some practices in place. We already had experience taking two different centers with two different philosophical bents and two different expertises, brought them together to do it -- not easy, because one center has to have the power of approval, and the other center is basically subservient to them, adjunct or contributory, but not in the position of power, and that's not easy because you have to get those people to buy into this, to share their expertise, to share their time, to go above and beyond the call of duty to get it done, even though the application is being approved in the Center for Drugs. And it was approved, I think, appropriately in the Center for Drugs because the mechanism of action was due to the cytotoxic agent, and the immunoglobulin was the targeted agent.

We had to have two different project managers from two different centers work together to schedule joint meetings. We had to share information, share reviews. We had to discuss issues that might require input from both groups and be resolved. When the person that looked at the chemical linker and the actual linking of this agent to the protein, someone had to step back and look at the overall structure of that protein and say, "Yes, it still seems to maintain its quaternary structure so that it binds to the appropriate cell receptors." That's not easy work because neither group was accustomed to doing that. This was very new.

Unfortunately, hindsight is always better than foresight. This product was effective, but it started to develop toxicities early on that we had not predicted.

I think the public comes to expect us to approve risk-free drugs.

Here was a case where this product, given at high enough doses, exhibited some unexpected toxicities. When things like this are cleared from the system, they go through the liver, they go through the kidney, and invariably that's where the problem starts. You've got a cytotoxic agent that's concentrating in the kidney or concentrating in the liver. You've got an immunoglobulin which doesn't pass easily through glomerular filtration in the kidney, and it caused problems. They saw some toxicities that were a real problem, and this product hasn't been used as extensively as we thought it would, even though it did exactly what we expected it to do.

JS: What kind of a patient population was this tested on? I mean, what was our approval based on -- what kind of a patient population?

JES: It was effective -- I cannot remember now off the top of my head what the cancer was. It was approved for a small, select group of cancers.

JS: So when we see this in a larger group . . .

JES: That's the problem.

Oftentimes, a company can only afford to do a study in, and especially for cancer, maybe three or four hundred people. When it's approved and it goes into clinical use, it's used in a larger patient population, and that's where the problem hits us. You cannot design a clinical study to pick up a one-in-10,000 toxicity when you only test it in a thousand people. It just doesn't show up.

RT: Where you have an expanded use and problems arise, can that drug still be labeled or restricted to certain confined uses?

JES: Yes, and that's what we had to do. We had to go back and adjust that labeling, and companies don't like to do that.

When you have a warning that has to be added to the labeling because of a side effect or because of its lack of efficacy, the company has got to go back, redo the label, reprint them, market it with new labeling, and they've got to have their sales force go back and explain this to physicians and end users. That's an embarrassment to the company. It automatically reduces their market. It's not something that they enjoy, and that's a real problem for the agency.

JS: These issues with predicting the drug's effect in a larger population, certainly this has been a problem for Chloramphenicol, a good example. Right?

JES: Absolutely, absolutely.

JS: One-in-20,000 patients with serious blood dysplasias in the case of Chloramphenicol?

JES: Never could have predicted it.



JS: Even with a huge Phase III trial.

JES: And that's why the emphasis right now is on this post-marketing surveillance group. I think it's probably well deserved and to be acknowledged.

I thank David Graham in some respects. It always takes a sacrificial lamb to sit before Congress and say we're not doing the job, unfortunately, because sometimes the agency doesn't act until it's perturbed. It's unfortunate but it's true. Every agency I'm sure is convinced that they're doing the very best job that they can at that time, and it's not until you're perturbed and acted upon by an outside force that you do throw the resources into something that you hadn't anticipated the need for.

JS: At what point, though, as a regulatory official, do you identify a product as safe enough and useful enough to be retained on the market with the proper labeling, perhaps black-box labeling, and at what point is it not? For example, when you look at the situation with the COX-2 inhibitors, Vioxx in particular, how do we deal with this as a product? And we didn't take it off, FDA did not take this off the market; the manufacturer did. But in your opinion, is this a product that could or should stay on the market with the proper labeling, or not?

JES: I feel all products have a use, and the COX-2 inhibitors are probably a good example. A good case in point: when used appropriately, I think they do a great job. It is another way to deal with inflammation or pain without resorting to the higher doses that are needed or prolonged therapies that are needed like ibuprofen, aspirin.

Unfortunately, these things cropped up when the dosage was bumped up because it was being used for something else.

Do you know the COX-2 inhibitors were in the Division of Oncology being looked at for prevention of cancers in the colon, and they were effective.

RT: Is part of that problem attributable to practitioners using -- there's a term for it -- off-label applications?

JES: Off-label. I'll give you an example of drugs we use right now off-label.

Aspirin. It's used off-label all the time. Right? It's not just for headache and fever. We're now taking it for heart problems. If someone hadn't tried that, how would we know about it?

Minoxidil was originally discovered as an antihypertensive. It was on the market as an antihypertensive, and it was a third-line antihypertensive. Now it's used by a lot of us to keep the ravages of time and re-grow lost hair

Viagra. I was involved in the approval of Viagra. That was originally investigated as an antihypertensive as well.

#### TAPE 3, SIDE A

JES: Just to pick up where we left off a few minutes ago, Viagra was originally -- as a matter of fact, it was approved for erectile dysfunction in the Division of Cardio-Renal Drug Products. Whenever an application comes to the approval stage, it requires three

signatures: the clinical division director, chemistry or manufacturing person, and the toxicologist, and I signed on that, I signed off on that. As a matter of fact, I sent that application back for some additional review because I thought they'd missed a few things. But that was approved in the Division of Cardio-Renal Products, and then it was moved over to the urologic group. And from here on out, all the rest of the erectile dysfunctions were approved over there. But the original review was done as an antihypertensive, and they discovered a very interesting side effect. I'm talking about the blue eyes, of course. [laughter]

Let me tell you, when that product was approved, there was such a run on it that they had to ration the product. It was being rationed at the pharmacy level.

You know, for a lot of folks, this was a salvation.

The company, Pfizer, was only making it at one plant up in Brooklyn, and it couldn't keep up with things. And one of the first shipments out was actually hijacked. I'm serious. And to my understanding, they're still looking for a group of hardened criminals. [laughter]

JS: Bad, very bad.

JES: We had to look at the post-approval changes on that drug incessantly for the first couple of years. They just expanded production all around world, and that was all work for the agency. When they put a new plant up in Kuala Lumpur, somebody's got to go out there and look at it, someone's got to evaluate that the manufacturing is the same one that they've used in the Brooklyn facility, and then we've got to sign off on that. So

when a product becomes a blockbuster, it often generates lots of additional work at the agency. Any product that's successful does that.

And that's one of the challenges, if I could editorialize, for the agency, is to try to streamline that process so that companies can expand their production without us encumbering it too much. That's a challenge for the agency because we're conservative by our very nature. We look at the data, we need to be convinced, we need to understand what they're doing before we sign off on it, and I think that's one of the areas that PDUFA I think will probably venture into, is this streamlining process.

JS: Quickly, going back to the issue with combination products that we were talking about, a couple of questions.

One is, you said that in the case of Mylotarg, that the Center for Drugs was the approving center in that case; and in the case of the stent, the Cypher drug-eluting stent, which center was it?

JES: Devices.

JS: Devices was the approving in that case.

JES: That's right. And we now even have an Office of Combination Products. Mark Kramer is a great guy. I've worked with him very, very closely.

JS: And when did that office begin?

JES: It's probably only been in existence I'm going to say maybe four or five years, I guess. It became obvious early on, when we started working with Devices, that, while Biologics understands therapy, therapeutic drugs, Devices didn't. The combination product using a device and a drug really represented, to me, the groundbreaking from the standpoint of getting two people that don't understand one another.

When we started working with the Center for Devices, they rightly understood that. They did not understand the drug portion of this device at all. They had been wrapped up in looking at the technology involved in taking a metal matrix, collapsing it around a rail, getting that rail to deliver it into the heart, and then expanding it with a balloon and leaving it in place. They had that down pretty well.

But when you take a stent matrix like that, a little wire matrix, when you put on it a drug and some sort of device or some sort of a matrix to slowly release that drug, all of a sudden they ventured into something they had no experience with. And they had good engineers and they had some good clinicians and they even had some good people like Leroy Schroeder, the polymer guy. What they didn't understand was, once you put a drug into that, you're now delivering something. And guess what? You can't take it back. You can't recall it.

So we started having joint meetings with the Center for Devices early on. We set up regularly scheduled meetings every two to four weeks. Our reviewers would look at the drug, the drug substance, how it was put onto the stent, what its stability was, how we measured the elution from that stent; and the Device people looked at the support, the architecture, what were the failure rates, how did they put it onto this delivery -- they call

it a rail-delivery technology where they have a long, very long, thin solid core that can be snaked up through the vasculature into the heart, and then it's inflated with a small airbag that pushes this stent apart, out-crimps it essentially, and leaves it in place. Then they pull the rest of it back out. But once it's in there, it's now a device to hold that artery open, but it's also a drug-delivery device. It's got in it some sort of a drug that does something at the interface with the arterial wall.

The problem was, every time they put one of these stents in place, you're essentially in contact with the sides of the blood vessels all the way along, and you're expanding it, taking that blood vessel and puffing it out with an architecture. Well, any self-respecting artery would try to repair that damage right away. So the cells on the wall of the artery would start growing rapidly and we'd get what we call restenosis. These cells would start growing right back into the stent. The stent was a beautiful matrix for this stuff to happen.

So somebody got the bright idea of putting a drug onto it that might suppress that proliferative cell growth. We tried an anti-rejection drug and then we tried an anticancer drug, taxol. I was involved with both the Cypher and the Taxus stents, and we did them in an identical fashion. A group of experts from CDER and a group of experts from CDRH would get together periodically. There would be a moderator that would lead the discussion. We would talk about manufacturing issues, we would talk about drug-therapy issues, we would talk about labeling issues, we would talk about efficacy issues. Here was a device that delivered a drug, and it had to be labeled not just as a device -- how to put it in, how to insert it, how to take the apparatus back out -- but were there now problems? What happens if the drug released too quickly or if the drug wasn't effective?

What did you look for? How did you label it? Did you label it as a device or a drug, or both?

Well, we had to compromise. We had to work our way through that. We had to find that some of the very contraindications that we knew this drug possessed still were in effect even though it was on a stent, and even though it was a very small amount. And we found that there were some thrombolytic problems, that some of the things that we knew about with the drug itself were still going to be involved even though it was a drug-stent combination. And that was an interesting, very, very laborious process. It took a lot of effort, it took a lot of time, it took a lot of meetings, and the real rub was that the company, Cordis, wasn't used to dealing with CDER people. When we would ask them questions, they looked like a deer in headlights: What are you talking about, measuring the elution of this from the stent? They're not used to doing this.

So Johnson & Johnson came along and bought them for that very reason, because they'd brought the drug experience with them. But some of the early discussions with the device firm, Cordis Labs, didn't go well because they didn't have the experts there that understood what we were talking about.

JS: Then that seems all the more surprising. I don't know the technology of how the drug is put on or in a stent -- but clearly, they had to have some idea unless this was completely contracted out.

JES: They had some idea, but they didn't understand that once you call something a drug, that there were regulations and requirements that came along with it.

For instance, when we approve tablets, we expect the first tablet and the ten-millionth tablet to contain exactly the right amount of drug, and deliver it -- dissolve and be absorbed. These folks, since they were doing developmental work, had done a lot of the development work by hand. They took a stent and they sprayed it, dried it, sprayed it again. Well, in a manufacturing venue, you had to treat all 10,000 of them that way. You have to make sure that all of them have the same amount of drug on it and deliver it the same way.

We sent our reviewer out on an inspection with the device inspector, and the device inspector was walking through the plant, and the drug reviewer took one look at what they were doing and went, "Wait a minute. What are you doing?" And they talked to them and they found out that each one of these stents was really an individual work project, and they said, "Wait a minute. There's no consistency here." Well, the device manufacturer and the device inspector had never really been involved in something like that before, so we had to retrain them to be sensitive to some of those issues. And we eventually got a product out on the market.

But today, to this very day, it still does not have a very good shelf life because the problem of putting a drug, a very small amount of drug, a very thin film, on that stent hasn't quite been overcome yet. They've automated it, but the polymer matrix that they use to glue that drug around the stent doesn't quite release the drug in a consistent fashion.

RT: Have some of those stents had to be removed and replaced?



JES: To my knowledge, no, but there were some deaths. It wasn't due to the drug on the stent, but, rather, a problem they had in the manufacturing.

When they put this tiny little -- you know, we're talking about the type of thing you have in your ballpoint pen, the spring. That's about the size of it. That's how big they are.

When they have the drug on the stent and the stent is finished -- it's dry, it's ready for incorporation into this finished package -- they take this balloon and take the rail that it's on, and they re-crimp the stent around the balloon and they spot-weld it so that it stays on there, so that when you start to insert it into the artery, it doesn't slide off. Some of the early ones, when the balloon was inflated, the stent wouldn't break free from the rail, and we had some people die on the table. That was a manufacturing issue. It was a physical manufacturing issue. It didn't involve the drug on the stent, but, rather, the complete package. And that was an embarrassment for us because they had to recall, I think, a thousand units right off the bat. We've worked through that and gotten that done.

But one of the problems that we're having is, here you've got this little matrix, this wire matrix, and you put the drug on it and crimp it onto the assembly, and you package the assembly and you sterilize it. What's the impact of the sterilization on the drug that's there? And what's the long-term survivability of the drug on that stent? And normally, when you pick up a bottle of aspirin, it's good for a couple of years on the shelf. The stents aren't like that. The stents have a reasonably short shelf life at this point. And much like yogurt, they have to be used up within three or four months. And there are still some issues that we haven't quite come to grips with on those, but that's -- I'm sure we'll achieve it.

But there have been now some bright people who have come along in the second generation of these drug-eluting stents, and now, instead of taking this matrix, this metal matrix, and spraying something onto it, now they've actually designed little reservoirs all along the stent, tiny little reservoirs about the size of the end of the pen point, where a tiny little bit of drug in a polymer sits, and it kind of sits protected. It doesn't get abraded when you insert it, it doesn't peel off, it doesn't slough off. It's in this tiny little reservoir hole, and it elutes from the front and the back of that hole and it does its job, and it does it nicely. But it took engineers thinking about the best way to put that drug onto that stent. We're finding out that it's not better to coat the whole wire matrix with the polymer now, but, rather, put it in a little reservoir that's protected. But they put a thousand of them on there. It's fascinating. You actually have to inspect them under a microscope. They take a look at it and they roll it under a microscope and they see that each one of those little reservoirs has a little piece of polymer that contains some of the drug.

RT: That research now is industry based. Is that correct?

JES: Yes, that's right. We're not doing that.

But the initial working-out of how we were going to approve that, resolving those problems, and making the company understand that those problems were real was a fascinating issue, because device manufacturers just aren't tuned into that. It's a screw, it's a stainless steel screw, you screw it into the bone, and that's it. As soon as you put a polymer on it and it's a drug, guess what? You've got a whole 'nother series of problems you have to deal with. What happens if you start to screw it in and the stuff strips off?

So it was a very interesting review and approval process for us, the Center of Devices, and for the agency. I think we're doing a better job.

RT: Did we cover those areas?

JS: I think so -- the three particular products.

Oh, one thing I wanted to ask, just so we have it on the record. Do we know about what time each of these products came on the market -- Gleevec, Mylotarg, and the Cypher drug stent?

JES: Oh, boy. Gleevec I think just celebrated its fifth anniversary. And the Cypher stent I think has been on the market now since 2004.

JS: Since 2004.

JES: Correct.

And the Taxus stent was probably about six months after that.

RT: I wanted to ask -- as the administrative leadership of commissioners, associate commissioners, Center directors, and so on, have you seen a trend or progression toward better science in the agency? Can you comment on that?

JES: Yes, we have. I think so, and we talked about the combination products. Now there's an associate commissioner for that. There's an Office of Combination Products, and I think Mark and his staff has done a marvelous job.

Unfortunately, there's always professional jealousy, and I think initially there were some hard feelings, friction, differences of opinion between the centers. I've got the power of the pen, I'm going to approve this product, so what I want from you is your opinion. I don't want you to make problems. I think the Centers are now working better together than they did initially. I think they understand that each center has an expertise that they bring to the table, and the only way you get these approved safely and effectively and quickly is to work together. So I think that initial problem has been worked out. And I think, actually, through the leadership of the Commissioner's office now, because the Commissioner's got to sit the two Centers down and say, "Look, I want this solved, and I'd like a report back." But the Commissioner has to take that leadership role. I think the two Centers, as co-equals, need that third party to force them to sit down and communicate. I think they both understand, but someone has to set that goal.

JS: And now it's the responsibility of the Office of Combination Products to provide that kind of direction.

JES: They have done a marvelous job.

For instance, they now have people that try to decide what the primary mechanism of action is. Sometimes there's a dispute. Was the stent an architecture to keep the artery open that had a drug there to prevent restenosis, or was the drug there and

the stent was just a delivery device? I mean, you can argue both ways. Someone has to make that determination. What's the primary effect? Is it a device effect? Is it a drug effect?

RT: As we look down line, a number of the recent, of the more recent, Commissioners have been either medical practitioners or other professionals. That's probably the way we'll continue to go, isn't it?

JES: It's interesting that Andy Von Eschenbach has been deemed the Commissioner. He's one of the few who's actually got hands-on clinical-trial development experience. It'll be interesting to see how he handles things.

I knew Andy before he became Commissioner. He was at M. D. Anderson for a long time. I had some interactions with him. That's not an easy transition because the Commissioner's got scientific issues, but mostly issues of administrative and people issues, not science. I've found that the science is always easier. It's the people, getting people to work together, that's the real issue.

JS: Did you know him when he was at M. D. Anderson as a clinical investigator?

JES: Yes.

JS: I see -- a connection with some of the investigational drug studies he was in?

JES: Well, as a matter of fact, Richard Pazdur, who is the current director of the Office of Oncology Products, was also at M. D. Anderson. I didn't know him, but I knew Von Eschenbach from my days in Pittsburgh. It's interesting how paths cross.

JS: We wanted to make sure that we covered the key issues that you wanted to cover, too, because I think you might have had some things in mind that you wanted to talk about.

JES: I do. I have a few things, if you're interested in them.

JS: Please.

JES: One of the things that I'm particularly proud of is this process analytical technology issue as part of this critical path, shortened critical path.

One of the things that we've been talking about at the Center for Drugs and the Center for Biologics for the past three or four years revolves around this concept. Because drugs are heavily regulated, drug manufacturers are used to doing this: manufacture the drug to point A, pull samples, take it to the lab, analyze it, come back, and then proceed from A to B, from B to C, from C to D. They will do things in a stepwise, sequential manner. With the analytical testing in between -- we call that batch processing -- process analytical technology brings the analytical method right to the manufacturing line, and they can monitor in real-time whether that product is ready to go from step A to step B and nip it in the bud if there's a problem in real-time.

I was part of a group that pulled together reviewers from new drugs, reviewers from generic drugs, reviewers from animal drugs, reviewers from biological drugs, together along with investigators and compliance officers to train them for about an 18-month period of time both in lecture and hands-on practical exposure to process analytical technology. We certified our first PAT team in the fall of 2005, and we got a Commissioner's award for that. We're still waiting to see the payoff.

But the idea is that this type of manufacturing is so seamless that it requires technical experts as well as technically trained investigators to go out and look at the facilities to see how it's being done and if it's being done appropriately.

The strength of this is that you don't throw lots of drug away. If it's out of compliance, you stop the manufacturing at that point and you adjust because you've got real-time monitoring. It's a real interesting concept, and we're encouraging firms to do it, we're encouraging firms to modernize and incorporate this type of technology in their manufacturing, and I was really proud of the fact that I was involved in the implementation of that. I felt very good about that.

And it'll be interesting to see if over the next four, five, six years, whether companies really do take that leap of faith into it. Some of the companies that have been calling me are people who want to know just how to proceed, and they're afraid to approach the agency to talk about it. So now they can talk to me, bounce some of this off of me, get a read as to whether or not this is going to pass the laugh test. And I'm really getting a kick out of doing it. It's really enjoyable to sit down with a small group like this, with the company's experts, and say, "Yes, I think this will fly. I think you're on the right track. But let me point out a few things. There's going to be some questions asked

about this, this, and this. You have to be prepared. If you don't, you're going to embarrass yourself." So it's interesting, the role that you can play to see that happen.

I'm waiting to see how many companies do get into that type of manufacturing, how quickly and what savings will be realized.

JS: Where did the concept originate, in the agency?

JES: Actually, it's arisen from other manufacturing areas. And the key is that drug manufacturing is heavily regulated. In areas that aren't as heavily regulated, for instance, a manufacturer of foodstuffs, every Oscar Meyer wiener that comes off the end is not analyzed. They have online technology that makes certain that that wiener that's coming off is ready for consumption. There's no reason in the world why we can't adapt some of that technology to drug manufacturing so that we can ramp up manufacturing quicker. Maybe one plant can supply the whole world if it makes it 24/7. But if you've got to stop the whole process and analyze it, that causes you to look at a different set of economics. So it's going to be interesting to see if those applications for other types of manufacturing will be utilized in the drug manufacturing process and the device manufacturing process.

GS: Technology transfer.

JES: Technology transfer. It's interesting.

And it was nice to be part of that, part of the inception, part of the discussion, part of the guidance, and part of the training. It's neat. It's neat to get to that point where you



can step back and say, “This is a pretty nice piece of work that we’ve got here.” So I’m very proud of that.

The other thing that we haven’t talked about at all, and I think it’s terribly important, is the agency doesn’t do a very good job of projecting, interacting with the scientific community, and I’ve worked tirelessly to do that. How many times have I gone out and spoken in the past? I mean, to be able to talk about what we’re talking about here, PAT [Process Analytical Technology] technology, to the greater scientific community, people that work in the companies, you know, we have to do a good job of doing that. You have to convince people that you’re open to that change, that you can do it in a logical, stepwise fashion, and that there may be some bumps in the road, but ultimately your goal is to get this technology out there. And as an agency, sometimes we don’t do a very good job of doing that, and we don’t do a very good job on a personal level like this or on a national level, and I think that’s something that I would really like to see fostered, rewarded, and done in a systematic fashion. You know, if we’re going to talk about critical-path initiative, the Center director or the Commissioner shouldn’t be the only one talking about it. It should be done mano-a-mano, at the scientist-to-scientist level too, because that’s where the rubber hits the road.

Critical path is kind of a very ephemeral idea. What does it mean? You put PAT technology into place here, here, and here, and all of a sudden your manufacturing doesn’t require much adjustment at all, does it? That’s what it takes. It takes showing people case studies, real successes, how to do it.

RT: Do you think that the Commissioners, plural, tend to suppress that?

JES: I'm not sure suppression is the right word. Maybe . . . You know, it goes back to this rewards thing. How do you reward people for doing stuff like that? How do you make people aware that this is important to them, to you, and to the agency and to the country? How do you do that? You know, you have to raise the visibility level, you have to show some rewards to people, not just the Center director or the Center director's deputy, but you have to drill down to the people that do this stuff and show them that you mean business, too, that you reward them, you encourage them.

Whenever I travel, sometimes I feel like a criminal. I come back and I have to document every penny I spend, and sometimes I don't get reimbursed because I didn't document it appropriately. The way to encourage me to do this is to say, "Hey, look, how much money do you need? Go do it. At the end of the year, one of the things I'm going to ask you is, 'John, how many times did you talk about this in a scientific venue?'" Countless times. You can do it, but it has to be done systematically. It can't be done piecemeal, and you can't do it just at the top.

JS: Right. Well, you'd be pleased to know that there was one conference I attended at the Keck Graduate Institute in April. It was a symposium on the drug regulatory process. And we indeed had a speaker from CDER -- Dr. Shirley Murphy -- who came out and spoke to this group about critical path.

JES: Oh, yes, sure. Super, super!

JS: And she talked about pediatrics and critical path.

JES: Super. I'm glad to hear this.

JS: So the word's getting out there, maybe not as quickly as we'd like, but it is getting out there.

JES: I mean, you know, the other thing is the agency doesn't have all the answers. It's an iterative process. We're going to make some mistakes, but we have to take the risk and try it.

RT: Well, I was just going to observe that this probably is part of the transition of the agency from the old autonomy where you didn't . . .

JES: That's right.

RT: When I first joined the agency, I was in the Federal-State Relations Office, and you remained a plebe a long time before you could go to a meeting and say anything of significance to state people.

JES: Yup. You've got to be careful what you say.

RT: I assume that is pervasive maybe in the other areas of the agency.

JES: I've been in meetings where I've been up at the podium and I say something, and I see the last row get up and head for the phones. I say to myself, "Geez, what did I say? Holy smokes!" you know. It's a funny feeling.

#### TAPE 3, SIDE B

JS: But when you were talking about the issue with the agency communicating to the outside scientific world, you're speaking even more broadly. You're talking to scientists and industry scientists and university scientists everywhere.

JES: That's right. And the public.

I don't think the lay public understands risk at all. What's the risk of taking this, what's the risk of putting this device into my body? I'm not sure we do a very good job of projecting that. When we approve a drug, if you give it to a thousand people, 800 of them may get better, but 200 of them may have problems, and we don't really communicate that well. We kind of raise these expectations to the American public that everything's risk-free, and it's not, it's not. We don't do a very good job of doing that.

JS: How do you think we could improve the job as an agency?

JES: One of the hardest things -- you know, we hire people that have a scientific expertise that's focused, and bring them here and we try to broaden their vision a little

bit. Scientists and physicians aren't very good at this. Sometimes it takes people like you to step back and maybe bring it down to the level that everybody can understand, not just at national meetings, but at high schools and colleges and universities, because somewhere out there there's a kid who you'll excite about it, who may grow up to be a regulator, not by default but because they want to. So we don't hire people that have those kinds of skills, unfortunately. And I'm not great at it. I'm okay, but I'm not great at it. But I enjoy doing it. I think it's something we need to do. It's important for us to think about things like that, not just the science, not just the administration, not just the budget, not just working here, but beyond that. How do we project? How do we communicate? How do we instill? How do we make people understand? The very same people that are frightened to death about taking this brand-new drug will get in their car, jump onto 270 and do 75 miles an hour from Frederick to Lake Forest and not understand what those relative risks are at all. And we pay the price for it because we get, when we make a mistake, we look ineffective. It's unfortunate.

RT: I think there is progress, though, in this general area of public education and cooperating by government regulation through consumer affairs officers and so on in the field. But they may not have on their agenda the discussion area that you're describing.

JES: I agree.

JS: And in the area of diminishing budgets, I know our public affairs specialists are out there doing as much as they can with the funds they have, but perhaps a little more would be appreciated.

JES: I know. That's always been a problem -- finding a balance is never a static thing.

The other thing that I think we really have to think about is the larger global issue, this harmonization issue. You know, in some respects, the drug companies and device companies are way ahead of us. They've already got facilities around the world. We have to get better intercommunicating with other regulatory agencies so that we're on the same sheet of music, we do things the same way or similar ways. It's very painful when I hear that Europe has approved something before we have, and I often wonder why; or we've approved something before Europe has. Why, why is that? Is it because the companies have targeted that approval to that population, or is it because they feel that that's a better venue for them, or is it that we're not communicating well between regulatory agencies? There's no reason in the world we can't be sharing efficacy data and safety data worldwide, because we're finding that different racial and ethnic populations react differently to these things. We need to document that.

You know, I was involved in the approval of Bidel. It was the first drug that we approved with a racial preference, hypertension in black Americans, the first time we've done that. Why? Why is that? Why haven't we looked at that before?

Asian populations have different metabolic profiles than ethnic European populations.

We've got to start doing a better job of sharing that information because, guess what, the world is shrinking. We've got people emigrating here from those very places, and that's something that I think we need to do a better job.

JS: Well, we've covered a lot of territory. Thank you for your patience.

RT: We really appreciate this interview, Dr. Simmons. You've covered an area that we don't have a lot on.

JS: We enjoy filling in gaps in our record in the oral history, so this has been a huge contribution to that corpus.

JES: I hope I can continue. And if you need to expand on anything, I'm available . . .

RT: Thank you.

JES: . . . to talk more about something.

JS: Wonderful.

JES: Sharing information is what it's all about.

JS: Thank you so much.

RT: We wish you success in better coordinating the whole effort in your private-sector activities.

JES: I hope so. I hope it proves not only to be fun and exciting, but useful.

RT: Okay. Well, thank you.

END OF INTERVIEW