Contrera, Joseph 2003

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Dr. Joseph Contrera
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Interviewer: Sara Shostak

Sara Shostak: Okay, you're aware of the fact that I'm taping this conversation.

Joseph Contrera: Yes.

Shostak: Great. Thank you. I was hoping we could start generally; and if you could just tell me about your background and what your position is here at FDA.

Contrera: Well, I can tell you about what my position was during the time we were engaged in the transgenic ICH, which was different than it is now.

Shostak: Okay. That's helpful. Thank you.

Contrera: At the time, I was a supervisory pharmacologist in the Division of Neuropharmacological Drug Products at the FDA, so I was -- in other words, I was a team leader -- one of the reviewers in the area and I got involved in ICH activities right at the beginning of ICH [International Conference for Harmonisation] in 1989 or '90. It became clear that, at the time we didn't realize how much impact these might have or how successful it was going to be. It became clear relatively soon that a lot could be accomplished in really fairly short order because of the way the organization was put together with regions and time lines, and it was really an intensive kind of a structure. It wasn't a typical academic debating society with no endpoint. This one was something quite different when we got involved in it. And it was like a freight train that's moving along the track, and the world being broken up into only three regions, mainly regulatory: Europe, Japan and the US, essentially, and the regulatory and pharma groups. That's it. And because of that there were agendas. There were topics that people had agreed on that needed harmonization, understanding in chemistry, quality area, which was chemistry, manufacturing, and then safety which is really the pharm tox, and then in efficacy in clinical trials. So there were those three areas.

So I was in the safety group -- pharmacology, toxicology, pre-clinical, each group had identified areas in which harmonization really was needed to be accomplished; standards that were close but not the same, redundancy, wasted effort, and going to -- we could see it evolving into a global economy, essentially. That was really the beginning of it and acknowledging that things were going that way. So I got involved in developing [unintelligible] -- it wasn't just transgenic. We were involved in dose selection for carcinogenicity studies. Whether or not one year non-rodent studies were evaluated, should be whether the duration of non-rodent studies should be one year or six months because there was discordance. Europe said six months; we said one year -- all kinds of issues like that that needed to be settled. We realized that any of these issues, and one of those issues and the major one was carcinogenicity studies. That was the biggest one, and we didn't tackle that right on, but we tackled it in the middle of the ICH later on, and that was, "Do we need a two-rodent? So what." And the European view was one was enough. The mouse—you didn't learn much from the mouse. The mouse had a lot of false-positives, and if we could do without it we could do [unintelligible]. And that was the European objective and goal, and they were fairly clear on running that as an endpoint in mind and we would agree on that harmonization. That was the type of thing it was. These things were on the table and they were fairly strong arguments. "Do it my way." "No, do it my way." And we would say, "No," and that was exactly -- it was really, really very contentious sometimes. But it turned out that we realized soon after that this was either going to be a battle, a verbal battle -- I mean a war. We needed scientific information, some basis for coming to these conclusions of which standard was better, or did it really matter? Sometimes it was irrelevant. You can pick either one. They weren't both were ineffective or adequate or whatever you want to call it. And so we realized that we had to develop databases, we had to collect information because it boiled down to a he said/she said kind of a thing. They said, "No, we should do it our way." We have experts that say, "No ours is better." And so do we have any quantitative ways. The same thing happened lead us to the transgenic. It was, how do we make a case for which standard was better? How do we make a case for the mouse? Is the mouse really irrelevant? When have we ever regulated on the basis of a mouse that was positive and a rat that was negative? What did we do? And no one had ever gone back and did retrospective analysis of the records of past history simply because there was no -- certainly at that time everything was paper documents and no one really cared. The way all the regulatory agencies and even the industry are concerned, you're concerned about getting a drug through on time. But once a drug is approved, it goes into a black hole, the file, never to be seen again. You hope you never have to look at it again. And you work on the next one that comes in. That's the latest; it's an assembly line. So there was no reason and no incentive for the regulatory agency or even the companies to collect this information, to develop a database, as to what has been done in the past until ICH came along, because all of a sudden we said, "How are we going to make a case for the rat? Are they right, for the rat, for the mouse, for the two – if we don't go back and see what happened? What have we been doing for 20 years with these studies? How have they impacted the drug-approval process? Did they make any difference, or is the mouse irrelevant?" In that case, they're right, you know. I got involved in database development, and that's my present job. Right now I'm directing a scientific database group and a modeling group because we started . The first database we developed was our own carcinogenicity database. We looked at all the studies that have come into the agency, going back into the late '70s, trying to tabulate them as to what they found and then trying to figure out what the regulatory implications of the findings were. What did the agency actually do with the information? Did it stop a drug from being approved? When? Under what conditions? And it was a crash course in doing this at the time because we realized that to make any kind of argument; we're going to have to have something tangible. They had experts and we had experts, and everybody was pontificating, but you know no one – the basis of it was anecdotal. "I remember" didn't do anything, you know? And these experts would say, "Oh, I remember three times where it did that." And so we really had to do something. So we put in an enormous effort -- I did, these groups -- to make the deadlines, because there were deadlines. The way ICH was running was that the topic is accepted, you start to discuss it, and everybody gets their viewpoints. It moves along. And there is a proposal, wording, and if you can't stop this, if you don't come up with a compelling argument against it that is able to change the decision points it will come out the other side and be approved. In other words, you'll just -- they'll get their way.

Shostak: They?

Contrera: They meaning whatever the alternate argument is. So that in the case of the rodents if we couldn't make a strong enough case to convince everybody that the mouse wasn't the one, the rat, mouse would be eliminated. But something would happen, in other words. It wouldn't be like an academic exercise where we go back and think about it some more or we go back and get some more information, revisit it in three years; no. There would be an action. It's either yes or no, but it will be an action. And so the action would probably have been, the mouse is eliminated. They would have the foregone conclusion in their mind, and in their mind, being the EU -- and the Japanese were sort of in the middle, and I think they were sort of sliding a little. They were always the swing vote in the operation. They kept sort of an open mind but they listened to both sides, but it was mainly the US and the EU were always battling each other, and always at opposite ends in many of these issues. So that was the basis, the background, for what happened with transgenic. Myself and Joe DeGeorge -- Joe DeGeorge was the associate director for pharm tox at the time at CDER, so he had the regulatory authority, and he was our group leader at the time of the transgenic models. He was the CDER group leader for safety, and I was one of the people on his team. My responsibility was I went to the meetings, we were like partners in this group, but I was supplying him with the ammunition, the scientific ammunition, the database information, the retrospective analyses that we were doing to make the case, to support the FDA case. But essentially we had to do that, and we thought that -- it was sort of like a poker game. We thought the EU had a lot of information that they had gotten from their pharma groups there and they knew something and they were going to come up with 10 compounds. They all were positive in the mouse and nobody ever did anything, or something like that, and therefore it's irrelevant. And they didn't know what our hand was.

Well, it turned out, we went and put together all this as much as we could retrospectively, and it was very difficult. We had piles and piles of reviews and documents and trying to put together a critical mass of experiences and do it in short periods of time, I mean, like six-month and four-month intervals between meetings. And we created a strategy. We did find cases where the mouse mattered, but more importantly, that case wasn't as compelling. What we arrived at, the conclusion, was what -- Ray Tennant came out with a paper in the early '90s that essentially said that for human risk in carcinogenicity studies, the highest you could stratify the results of rodent bioassay -- you know, the stratification papers are really so basic, and it was well done, and I don't know if it got all the references and citations that it should. I use it a lot because that was really fundamental to our approach here, and it was articulated well in the paper -- simply that the carcinogens that have the highest potential of being human risks are those that cause tumors across species -- trans-species, transgender species, and you can almost rank these. In other words, you have carcinogenicity studies you can view as four-cell studies, four study cells. They're really four study cells. You have the rat, male, female, the mouse, male, female. Four study cells. Each one is an independent study you can look at and if the compound gives you positives every single cell. That compound would be at the highest ranking as a carcinogen and it would also have the highest likelihood of being a human risk because -- and it's not just across species, but it's also -- there's another factor called multiple-site tumor. So not only does it cause a tumor male/female mouse, male/female rat, but it causes multiple-site tumors. Now we have a liver and a kidney, going on too, so then you stratify. Then under that would be three cells, two cells, one cell. And the least likely, the lowest risk and the one where you're getting into statistical gray land is where it's just one sex, one species, one site. And so then you could stratify the results of carcinogenicity studies this way and as to most and least, and -- all right, if you buy into that. Now, I think that's fundamental in the way we do risk over here too, for drugs. Now pharmaceuticals have benefit / risks. So you don't just -- if you just get one small signal in a mouse doesn't mean the drug can't be approved. It's just not the way it works there. It is unlikely to be really a problem at that level. You have to weigh these things, the weight of evidence, and take that into consideration with all kinds of things before you make a decision. But the fundamental for this principle is two species you know, right? How can you tell? How can you know if it's a trans-species carcinogen of you didn't test it in two species? And it became so simple. And so then we created -- we constructed this -- that was really bulletproof. I mean the logic was so bulletproof, but it was really fundamental. It was based on Tennant's work, so it wasn't just something that we could cite it and say, "We have evidence for that," and it was a hypothesis that was simple and made sense.

So Joe DeGeorge and I really worked that. We said, "Well okay, this is an opportunity. It's a convergence of the stars at ICH for this, really," because we knew that rodent carcinogenicity -- people call this study the gold standard. It isn't. It's the only standard. How can it be gold if it's the only standard? And it's the only thing we do, and it was created almost ad hoc after the war on cancer in the Nixon administration. We had to come up with something and people just got together and said, you know, we'll use rat and mouse because we know a lot about rat and mice and they're cheap to build and then to grow. And it evolved -- the standard evolved, the dosing scheme evolved, and it wasn't something that --and it works, but to some extent it's been extended beyond its actual capabilities, its analytical power, statistical power. It's really limited. But everybody and the regulators embraced it and maybe extended it beyond where it should have been extended, you know, the results of the study and what they really mean for humans, because, after all, they're not humans and cancer isn't that simple. But, that said, we said, "Well now is the time where we could -- I think the study can be improved." And not only that but some reality has to be set in, in terms of its strengths and its limitations. People don't talk about those things. It's like the emperor's clothes. Yeah, we have a regulator basis, but does it really tell you much? And so we said, "Well, now is the time." NIEHS had just been working for a few years before that developing an alternatives to the transgenic model, and there was enough -- there was a core of information by '93, in that time, where we said, "You know, these look like promising models" -- the Tg.AC and the p53 knockout, and they had a core of information that showed that they had sensitivity and predictivity. A lot more needed to be done, but there was enough there that they were viable alternatives. And it was our feeling that it was time to try to inject some innovation into the carcinogenicity. It was way overdue, to try to develop better models or alternative models to the rodent assay. And since ICH, we were there, people were looking at the topic, and not only that but we were in an organization where something could actually happen. You know, it wasn't an academic exercise that we published a paper and it would go nowhere and then that would be very nice, but here people were interested. Something was going to happen. It was a real -- and we said, "Now's the time to leap forward. We have everybody's attention. They want to get rid of the mouse. Instead of getting rid of the mouse, we'll say, 'Yes, we sort of agree with you, but we really can't get rid of it totally because of the trans-species. We feel that for risk assessment we need trans-species information to really be able to at least filter out the worst carcinogens." And that's really all the assay is probably good for. You want to make sure you don't get nitrogen mustard out there. But in terms of the other kinds of things that we see creating tumors, the endocrine tumors, there's probably not going to be a whole lot of relevance to humans. We regulate them, but that's a gray area. But the assay should at least be relied on to get rid of really bad things, and it can do that. It can get really, really bad; it's the gray areas that we argue about. So we said, "Now's the time." They want to get rid of it, we want to keep it, but maybe we can come to a combination, you know, a middle ground, and everybody wins something. So we came up with the alternative proposal. We made a compelling case that you need the trans-species..

Shostak: "We" was you and Joe DeGeorge?

Contrera: Yeah. And the FDA team made the case. I think the Japanese agreed with us. Then they said, "All right. What about the transgenics?" You know, they hadn't been validated. "Yes, promising! But they hadn't been validated. So then we brought up the point and then we made it clear. "Let's go back to the record of the two-year assay;" and it has never been validated. And we accept it because, at face value, it seems to be, you know. But there's no validation. People don't do it over again. It's a $2 million effort [laughs] and they don't even run positive controls in terms of known carcinogens running along with the study -- they don't do that. And with the transgenic, we forced them to do those things. And so they eventually acquiesced that that was the best thing we were going to get, that we would -- that there would be an alternative route, that people could do the two-year mouse or they had an alternative, not doing the two-year mouse but doing a six-month transgenic, and there were conditions for going one route or the other. So the driving force to getting the alternatives was the existence of a viable model, thanks to NIEHS, Ray Tennant's group, and the interest of the ICH in making a change and reducing the use of the mouse. Eliminating the mouse is really what they wanted. You know, the intention to eliminate the mouse was the driving force. So we reduced this so we could eliminate, and that's where it stands today.

Now, how the European Union actually functions in this regard is interesting. In general, they ignore the transgenic mouse in their regulatory process. So when a company elects to -- this is what I understand is going on -- that when a company elects to do a transgenic, it meets the US standard for two species and it meets the European standard for one species. [laughs] I mean, practically, pragmatically, they don't care about the one and they're still skeptical about the utility of the other one, so they don't bother; they don't look at it. That's their prerogative. But it's interesting how it went. But as far as the guidance is concerned, it's there, so we have an alternative. And we've been, since then, of course, fairly large, close to validations study on transgenic. The ILSI group, you know, we set up a series of compounds and then volunteer companies were testing them, and we put it all together a few years ago. The results were published. So we've gone towards greater validation of the transgenic in terms of what their strengths and weaknesses and sensitivities, and it's a first generation. But the important thing is that we finally broke, to break the hold of this gold-standard bioassay idea, because we want to open the door towards innovation, and transgenics may be just a small milestone on the way to totally different kinds of approaches that are coming in the future. But at least it opened the door not only in the process for how it can be done, and that it can be done, because it was like heresy. I mean, it's like heresy to even propose -- even now if you propose anything else but the two-year assay, you know, it's like people consider that you're risking the public health of the world or something -- an untried method. But you're in the circle. When you go to the pharmaceutical industry they hate the two-year study. "Oh, it doesn't show anything, it doesn't prove anything, it's worthless and it costs us a lot of money." They said, "Okay. We're going to come up with a new one. Here's a new alternative." "Oh, we can't use that. We don't know enough about it. We don't know how sensitive -- it may be too sensitive. We don't have the experience, it's too risky." Well, how do you go from here to there? How do you develop a new method and at the same time not run into the uncertainties of the new method because they were worried about their product. "What do you mean? I'm going to risk my product on some untested new -- what if it's positive? We don't know enough about this, the method." But the two-year assay, they have the game down pat. They know how to argue about the tumors and why they're not relevant. They've been doing this for 30 years and everybody knows it, knows how to argue about it and how to deal with historical controls and -- the new method, you don't have much historical history, you don't have experience, you don't know the mechanisms so much. You don't know -- it scared the hell out of them. So yeah, they want innovation, but they also want the security of no risk. At ICH actually it was amazing that we were able to get by at all on this thing because they were really, really worried. They figured, "Well, they just won't -- they will never propose it for their compounds. It wasn't mandated that they had to do it." But slowly, like everything else, we let the marketplace sort of take over. The companies are competing with each other, and some people start to use it and they say,"Gee, they're getting away with only a six-month study," and then they're worried about that it was going to be real sensitive, and now they're realizing it wasn't overly sensitive. In fact, now the regulators are arguing it's not sensitive enough. At the time it got -- you know everything was going to give you tumors in the transgenic, and it's not true.

Shostak: Did they think that both about Tg.AC and p53?

Contrera: Yeah. They got those two; you can use those, too. Right now the way the game plan is that the p53 looks like it's only really sensitive to genotoxic compounds that are positive in veins or -- so the way the decision tree goes is that you can't use it unless there's a positive in one of the battery, gene tox battery screens, and if it's not positive in that one, then they do Tg.AC. And now there's the H2 Ras, also, model. There are three viable -- there are some minor, but the Ras H2, the Japanese-developed model, is valid and the animals are available. They are starting to see some studies with that, and that's a good model. And it probably is better than the Tg.AC. There's always been a problem with the skin painting and partial brushing, but people use it. It's good for topicals. It's actually topical form. So that's where we are now. We hope that these are just the first generation of these animal models coming down, hopefully, with NIEHS doing its thing. I don't know if there are many centers out there that are working toward developing. And then there might be other, you know, gene arrays. There might be some other humanized animals in the future.

Shostak: Tell me what you mean by humanized animals.

Contrera: Well, we actually have an animal that has oncogenes that are actually from humans, so they -- because don't forget, the major tumor sites for humans are breast, colon, lung -- those are rare in mice and rats. Those aren't the sites. With the rodents, it's the liver. In humans, that's rare. So, they're the wrong models, really. I mean, if you go by site, then they're not the right model. And that's what I mean by how much you can extrapolate. The worst thing I think we can do from our experience in the area, in our database, looking at that, is to say, "Ah, we have a rat liver tumor. Look for -- make sure you screen people for liver tumors." It's not the way it works. All you can say is that it's causing cancer in rats. Look everywhere, whatever species, because there's almost no site specificity, even between a rat and mouse. There's very poor site specificity. But in the rat you might have a liver; in the mouse you might have a pancreas. It could be the same mechanism, but the tissues are different, the metabolic processes of the organs are different. We don't know. So the only thing you can -- the main thing you have to focus on is there's a tumor; it caused tumors in both. Don't worry about the site. The site will get you, I think, off on a tangent that will get nowhere. The main thing is that it may cause tumor in two species. That's what's important. And a lot of -- I think there are people – agencies that still regulate on the others they're chasing their tail with this -- but the idea is that if you can't extrapolate a rat to a mouse, a mouse to a rat, how do you expect it to extrapolate to a human? It may be by random, you just lucked out, but it's not going to happen that way. That's what I mean by the limitations of the model right now. I think some people are interpreting it way beyond what it was even designed to do by the very nature of the limitations of the model. I think they do a disservice to them in some respects. Or when they regulate on the basis of a single-site, single-cell tumor, and they say, "Well, this could be a human hazard," I think they're over-regulating because there is really a gray area. There is a lot of noise in these assays. Don't forget, you're dosing an animal for two years, and also in the last year of the two-year animals -- the animal only lives three years. That's fairly old. That's when you have all of the age-related tumors coming in. You have a high background in the area of tumors just by the nature of the animal. One thing that taught us a great deal in pharmaceutics that other areas didn't have that was enlightening to us is the issue of dual-control studies. I don't know if you've ever heard of it, but for pharmaceuticals, many of the companies design their two-year studies with two identical control groups. In other words, usually there are 60 animals per group You have your low, medium, and high, three-dose studies in the rat and mouse, and the control being untreated or vehicle treated. About 30 or 40 percent of our pharmaceutical companies -- and we don't force them to do it, but we know it, we encourage them to do it -- is they take two groups of 60 animals that are untreated instead of one group of 60 animals and say, [unintelligible]. The statisticians have a lot of problems with this and we fight with them all the time about how to interpret dual controls. But what we've noticed over the years in the results of these studies is that there's an enormous amount of noise in these bioassays, more than people realize. Sometimes you can have a tumor incidence in one control group, that 14 animals have a tumor, a spontaneous tumor. In control group two. In control group one, there's only two. Now how do you figure that when they haven't even been treated? And how could they vary so much? Well, that colored the way we looked at these studies. That's why we say the limitations of the power of the study of the bioassay is very -- it's limited the application. So if you can get that much variation between two controls how can you regulate on the basis of some -- of a just barely statistical, in one cell, and calling it a positive? You really are hazardous, over-regulating, going way beyond the power of the assay to do that. And that's why it colored our view in terms of what's positive. The assay, at best, is there as a safety screen for making sure we don't approve really strong carcinogens. But it has almost no way of dealing with anything else -- whatever is not strong, whatever that means, with classes of things that cause tumors that are relatively weak or species-dependent or endocrine-dependent you are in -- it's very hard to know what that means in terms of risk to humans or it's unclear.

Shostak: You mentioned that during the ICH process, it was fortuitous that the NIEHS had been working on the Tg.AC and the p53 models, and that they were promising, that they were viable alternatives.

Contrera: Yes.

Shostak: When you're looking at a model, a way of testing carcinogenicity, how do you evaluate whether it's promising or viable? What made those models attractive?

Contrera: Well, they had already screened something like 14 or 15 compounds, I think, that represented strong carcinogens and non-carcinogenic compounds, and it had at least gone through that first kind of validation. I mean, it certainly wasn't the whole universe of chemicals. But it had met the initial kind of standards that these were positive when they were supposed to be and negative when they were supposed to be, by and large. They seemed to be making sense. And then, mechanistically, the p53 had a lot going for it, because don't forget that was another big feature of the transgenic, is that these models for the first time could represent animals that, which the cause of the tumor was known. You could actually define a reason for the event; the p53 being an ideal model for that, because it was a hemizygous, one allele, p53 allele is knocked out of these animals, so carcinogen, the positive effect of that -- usually knocks out the second allele, so you knew exactly the mechanism that it was causing, what was actually causing the tumor; whereas in the two-year mouse there is no idea what the real mechanism is of the tumor effects. Nothing is known about that in the wild animal, the wild form of the animal. This opened the door for the first time of -- where you would have a mechanistic insight into the cause of the tumor. Not only that, but the p53 was a gene that was involved in over 50 percent of human tumors. So now you had a biological rationale for a model, a rational model that had human implications that doesn't exist for the wild type tumors in the two-year. Now that was like -- from a scientific point of view, was a light year step forward from the old two-year assay where you just throw in a drug and it's causing a tumor and you don't know what the basis of that tumor is and what it had to do with human tumors at all. And so it was like a light year. And it pointed the way -- this was the ideal. We could only get -- we'd have a whole array of all types of tumor sites of genetic loci that are important for human tumors and then design them into an animal.

Shostak: That's what you mean by humanized animal?

Contrera: Yeah, humanized animals. Yes, yes and you'd have the human breast cancer genes and you have all that and you'd develop this animal with all these sites that we know are important in human, and then you'd treat the animals, be it drugs, that are causing an effect. And we wound up actually regulating on the basis of p53, taking a drug off the market, early in that -- right after the ICH was approved. Phenolphthalein was taken off the market. It was just serendipitous that it happened at the same time; it'll probably never happen again. But it was a perfect example of the application of p53 because NIH had done the study and phenolphthalein caused tumors in the p53 animal, it caused tumors in the two-years, but they were low-incidence tumors, but when it caused tumors in -- that's in a rat, but when they did the p53 and it was positive, and then when they looked and actually it did knock out the allele. I mean, there was increase in p53 protein. It was like a perfect kind of a circumstance that proved the utility of the model, and it gave you insight beyond which you would have gotten when it was just an ordinary mouse study -- you know, with a tumor somewhere. This one said, "Well," -- our view was if the p53 is positive, it says that it's a human health hazard.

Shostak: Is that the only example of a chemical or a drug ?

Conterara: Right now.

Shostak: It has been regulated based on p53?

Contrera: Right.

Shostak: And have any been regulated based on H2 ras or Tg.AC?

Contrera: Not yet.

Shostak: But information from transgenic studies has been incorporated in a weight-of-evidence approach?

Contrera: Yes. It's used just like a two-year mouse. It's used as an alternative in our center. It's equivalent. We have a committee structure -- the Carcinogenicity Assessment Committee. It's a voluntary committee. It's voluntary to responses. They can submit their protocols. Their carcinogenicity study protocols to the committee. If they do, we look it over and we agree or disagree on the doses and the design of the protocol. And if we agree, they get a note from us saying that we agree on the doses, and from that point out there is a commitment to accept the study regardless pretty much. And that, I think, is something that the industry that's the best thing we've ever done from their point of view in the last 15 years. We set up this. It' s helped a great deal because it's helped to sort of nurture and guide them with the transgenic studies, because they would say, "they'll submit the transgenic protocol, and they'll get our view on whether the model was appropriate, the dose ranging, how it was done, the concentration of their positive controls, all kinds of things." So there's a lot of hand-holding, especially when it was new. And after that, then they do the study and we accept the results. So far -- again, if anything, it hasn't been a model, even though you'd think it would be a model that was very sensitive, getting too many positives. It's not turned out like that at all, which is what the companies fear. So now they love it because -- and the regulators are saying, "Gee, maybe it' s not sensitive enough." But time will tell. It just takes experience. You've got to keep doing a lot of them. But maybe it's just sensitive enough. Maybe for pharmaceuticals, they're really not designing into the molecule things that are causing much problems and maybe they're reaching the time where people know enough in drug discovery that could almost know about from the structure activity whether or not it's going to be a problem. Maybe we don't have to do these assays as much anymore. That's something we're working on now here. The whole generation, the next generation is now we've done what we're doing here, and this is our group now. This is a research group now -- it's much less regulatory. But we've developed a kind of model, low-carcinogenicity results, and clinical results for doing -- now that we have a large database, databases are fine, but now what we're trying to do is learn from them. So now we're trying to model the results, structure activity and relationships. And maybe you can develop predictive tools, computer-based predictive tools that will tell you that the compound is similar to many that are already marketed that we know a lot about, and it's unlikely to be positive, with a fairly high degree of certainty. And then, if that's the case, then maybe the resources involved in testing another acetaminophen or another antihistamine would be put to testing those compounds we know little about. We don't have much in our database that would really represent new things and not wasting all that effort, resources that are limited in testing the same old thing over and over, umpteenth statin and the -- you know. So we need a basis to make rationales like that. That's what we're working on now, is that maybe the next generation would be -- maybe they will eliminate. I'm looking forward that maybe carcinogenicity studies, the traditional ones, will be reduced considerably, but more on a rationale basis. And they'll be used for things where we really have data to get. So, I mean, that's in the future, nothing to do with the transgenic, but we're going beyond.

Shostak: No, but it's --

Contrera: Beyond new models and new approaches, different ways of looking at things, because we've been doing these for 30 years. I think we have a good sense of, at least if the structure is similar to what we've been doing for 30 years, the computer can do a lot of that modeling and give you a fairly good sense of probabilities that it's going to be a problem. And the fact is that it would really save a lot of effort if we could work out an arrangement where, okay, the money that would be spent testing the same old thing over and over again be used to test something, really be tested, because they're so new, they're not in the data set.

Shostak: They're not represented by the ….?

Contrera: Not represented.

Shostake: Assay.

Contrera: And we want to learn about them. So that's -- I'm expanding my interest in where I think the transgenic model, and we'll say, "Well, you can only do these and not even bother with the two-year. If the computer tells you it's not going to be a problem, then maybe you can go to tier in vitro and short-term tier." Now, if they turn out positive, you've got to go and do the other one. So different.

Shostak: One of the conversations that Ray Tennant and I have had ongoing for a little while is about in what ways the experience with the transgenic models is a precedent for or a natural history or a lesson that has applicability for developing other new models, and I'd be curious to hear your thoughts on that.

Contrera: Well, there have been a lot of lessons that we learned from it. One is the organizational structure that's necessary to make a change that's so fundamental and that influences both the industry and the regulatory community that it requires an organization like the ICH, a sort of commitment of all parties right at the beginning, and I don't know how often that happens. But the fact that it did happen kicked the door open that it can -- that you can change and develop innovative methods, and the way it was done in ICH is the ground, the plan for how -- it is a model for how you have to do it.

Shostak: Will you, just because I'm not as well versed in that as you are, can you tell me what the pieces are?

Contrera: You have to have industry group and regulators, core, key people that are knowledgeable, from both of those groups have to be present, and they have to be committed to making a change. They target a particular topic / issue and say, "We're going to -- at the end of this, we're going to make a change to prove the way we're doing this particular, whatever it might be, endpoint." So there's a commitment that something's going to happen at the end of this and you need a structure that actually has authority and commitment. It can't be just a study group. I don't know. The ICH was unique that way. Now, it almost slipped under the radar screen. Nobody took it seriously. All of a sudden it developed a real life and then you were run over by it. But you really need industry and the regulators to buy in and a priority saying that we're going to -- in two years from now, there's going to be a product. And this is the issue. In two years, we're going to have a product. And that doesn't happen very often, so you need it. It's like the organizational structure, but to some extent now, maybe ICCVAM. I mean, that was -- sort of came later on. But it represents maybe a forum for getting new methods to be accepted or evaluated by many centers, many regulatory organizations, so maybe you could get something like ICCVAM plus a pharma, or ICCVAM plus chemical industry. You put those two together, you would have an ICH kind of operation. There's some machinery -- so you need administrative machinery in place to get this done. But it set the road plan for how, that it can be done, this is how it was done. It's a model. There are other organizations out there, OECD and other developing kinds, but when it's something that is fundamental as the carcinogenicity study needs something that -- well with ICH it was only pharmaceuticals.

Shostak: Right.

Contrera: And maybe that's why it wasn't like regulating the world, in commerce and chemicals.

Shostak: But one of the things that I don't understand that I would like to understand better is because ICH was pharmaceuticals FDA was at the table but EPA was not.

Contrera: Right.

Shostak: And it seems – though I'm still trying to figure this all out -- that FDA has been much more open to alternative forms of testing, more open to the transgenic models than EPA has.

Contrera: Yeah, yes.

Shostak: And, well, I'd appreciate it if you could help me understand that difference. Is it just the FDA was at the table for the ICH, or what all is going on?

Contrera: Well, that's true. Right now, at the table, it was the FDA and pharma, and many of the FDA equivalents in Europe and their pharmas and Japan the same way. And so -- because it was just pharmaceuticals, human pharmaceuticals, not even veterinary and it only represented three major self-producing regions. It doesn't even represent the whole world. But Canada and Australia, they were observers. The World Health Organization was an observer. And maybe that's why it was successful. It was really a group made up of only the really interested parties, major interested, excluded -- it was successful because of what it excluded. And it tells you that you that if you want to be successful at getting something new done you can't involve too many people. People say you need total inclusion. That's no good either because you'll get chaos. And too much exclusion obviously is no good either. But if you want to get something done, exclusion works better than inclusion. And people could argue about it later and you can modify it later, and that's what happened. But there's a – you know, now you have OECD guidance for chemicals, and they say, "Well, this applies to pharmaceuticals, because chemicals are pharmaceuticals." That was -- things are meshed sometimes. We said, "Well, this is our domain," and we're still fighting over that right now. There's always going to be a -- that's the downside of when you do things that way. I don't know what to do with it, but I think if you want to be successful you have to have a core group that's really committed. They want to see something happen. They're knowledgeable and they really are dealing with the problem every day and then you get something done. Now, when you say the FDA, that has a lot -- there are centers a lot of here.

Shostak: Right.

Contrera: And drugs is the ones that really dominated the ICH. Drugs were to a major extent biologics were [unintelligible]. That's not all. Narcotics weren't there and devices weren't there. It was drugs, therapeutics, and human drugs. We didn't -- for example, foods. I don't think they use transgenics. So even within the FDA, there's not consensus on transgenics. I don't think they ever have accepted it, and that's FDA. So, in fact, we've had -- when we published the comments to the guidance, the transgenic guidance, I think we got more critical comments from our sister agencies than we did their industry. It was IRA [spelled phonetically] or the scientific community -- everybody sort of lauded us, but our worst critics were regulatory agencies because they're wedded to this idea.

Shostak: What was the nature or the tenor of their critique?

Contrera: "Two years is a. We've been using it for years, it works great, it's the gold standard. These things, we don't know enough about, how do they get validated," same old thing over and over again, and they just couldn't break out of their -- take a chance on something new. "We don't know enough about it. We don't have enough experience, they're not valid." They get the same -- it's what happens because they're regulators, you know. You don't hire regulators to create things. You get them to regulate what's there. They represent now. And so developing something new is not their domain, it's not their job. And maybe my opinion is on tape, but it's true. So it's a rare event to move it because to say that you're going to develop an alternative means there's something wrong with what you've been doing, and you're committed to this. You've regulated for 30 years. You've protected the public for 30 years from something and you've got to prove that this thing is better. How do you -- it's very hard to do because, in the end, we don't know what happens downstream in terms of human exposure. We really don't. I mean, the best model is humans for humans. There isn't any -- there really isn't. The rest of it is making do the best we can because we don't know any other way. So to some extent -- I don't know if you read my paper, a couple of papers that we had on the transgenic.

Shostak: I'll show you the one I do have.

Contrera: I go over that, because we're writing that paper it was a little bit difficult. It's difficult -- not a little bit difficult.

Shostak: This is the one that I have.

Contrera: Yeah, because at the time we wrote this paper, we had to tear down to some extent, but not do it in a belligerent manner, but you had to show the strength and weakness in what we're doing and validity in what is now, and then show how the alternative isn't that much worse or that it won't be that much high -- you know, risky for the general public. So you almost have to tear it down again to show, well, how good is what we're doing? Has it ever been validated? How specific is it? How sensitive is it? How relevant is it to human? And then -- so once you answer those, and say, well now, the alternatives. How much -- how different are they? And we had to sort of develop, make a case, because if you're starting with something that's perfect, and then you want an alternative to perfection, and you can't do that and then it's really hard. And that's almost, you know, what the regulators would say, "This is perfect. We've been doing it for years it's the best thing on -- it's the gold standard," and that always makes me irritated when they call it the gold standard. It's a standard. But how are you going to create something better -- if that's the gold standard, what am I going to do, make a platinum one? But we're saying it's poor, and it's due to -- we've got to find something better. That's our prerogative. I don't know what it is yet, but it's not so good. And if they -- there's got to be better ways of doing it now. But if we don't try, it'll never happen. But how do you encourage people to develop new models? There's no profit in that. Except for NIEHS -- companies won't do it.

Shostak: Right. So why does NIEHS do it when no one else will?

Contrera: I don't know. You've got to ask Ray that. I'm glad they did; I'm glad they did. I mean they have an operation there. They've been cranking out two-year studies forever, and they could make a living doing that, and to some extent they have. But in a way, that was the perfect place. While they have so much experience in the two-year assay, they represented a research base that should be looking at alternatives because they know the limits and vagaries and liabilities of what they're doing, too. Plus I think they realized the enormous amount of chemicals out there that need testing. And this thing is too long and too hard and too expensive, and the answers aren't so conclusive. You know, you get a lot of equivocals, but there needs to be something more efficient, better, and more predictive of the human. I think that became clear to them, I think, in the '80s. When they started looking for alternatives, I think that was a big thing. We can't afford to do these studies. Not only that, even at our current level, it would take us a century to -- there are a lot of things out there need to be tested and we can't get to them. Nobody's going to do it. We need something quicker, cheaper, and at least as good. And we were trying to make the case that this isn't that great. So at least it's good is a reasonable thing. But the people wanted validation about what exactly -- how many compounds have we found? I said, "Well, we have a hundred or so for the transgenics; a reasonable core." What do we have for the two-year assay when we adopted it? So that's really it. I think the same thing's happening now – pragmatic, resource-based issues.

Shostak: Can you help me understand what the connection was between the ICH guidance and the ILSI Committee on Alternatives to Carcinogenicity Testing?

Contrera: Well, ILSI just was a perfect -- it's a nonprofit organization that third-party group is used a lot as a forum in which the regulators and industry get together and develop something. From an administrative point of view you have a non-profit organization sort of in the middle of it, sort of running things, and they can collect money from industry to do it, so there are a lot of legal aspects to why it's practical to do it that way. It's easier than doing it directly, between the two of us. And they are always looking for issues like this, are what they do for a living -- ILSI does for a living. And so they' ve been used before for lots of other issues, regulatory issues that we -- they represent a neutral third party that can organize the meetings and place and all those things. And so they were -- it became clear that we had to -- we'd adopted the end models and that we needed to do additional validation studies more than NIEHS could do one at a time. So NIH was doing 10, 12 a year probably, though. We got together, interested parties and ILSI and companies, main companies and the regulators, and it was mainly CDER, FDA and the pharma groups that were interested. And the companies developed a list of compounds to test -- some that were negatives and some that were positives and they represented various categories of carcinogens, and then the group just went around. The companies volunteered to test these and they paid for it with their own money. And then we got together at the end and we got the results. It had taken like three years to put this thing together. I mean, it cost some money, the companies donated funds, and we donated. And so that was a perfectly normal outcome of ICH guidances; sometimes these are post-guidance kind of operations. We do that for other things too, not just in transgenics -- issues that we need to get clarification on additional work done. It's a way to get companies and the agency together. Everybody throws in some money in the pot, you know, and you get things done. And that's what that was all about.

Shostak: Okay. I'm curious how it is that you and Joe DeGeorge had become aware of the NIEHS research, the existence of transgenic models.

Contrera: Yeah. Well, we work with them all the time. Don't forget, we get all the NIH -- NIEHS's carcinogenicity studies here. We get routine mailings from them; look at their studies; we nominate compounds for testing, and they've tested some pharmaceuticals. So there's an interaction with them that existed years before. And so it was very easy to see what they were doing in transgenics. And they had published some papers on it. So there was an interaction -- always there because of the two-year studies. We've had interactions with them for all kinds of issues -- dietary restriction and all kinds of other issues.

Shostak: And a related, just how-things-worked question: how did you and Joe DeGeorge first become involved in the ICH? Was that a nomination process or an invitation process?

Contrera: By nature of our positions and experience at the time. It originally started -- when ICH started, Judy Weissinger [spelled phonetically] was the associate director for pharm-tox at that time, in '89 I guess, when the ICH started. And she conned me into being part of it, and at the time I didn't know what I was getting into. And to do -- what was the first? I don't even remember -- dose selection? I don't know. There were a series of ICH objectives at the time.

Oh, I know what it was. How could I forget it? We had a dog, a non-rodent, duration of non-rodent toxicology studies, 6 months and 12 months. That one turned out to be the worst possible, and it's still not settled actually, and I probably made it worse, but that was my first naive attempt at getting involved in putting together data sets, and the Europeans wanted six-month dog studies and our rodent -- their duration was six months. The U.S. had always been a year. So we had to come make a case for why the last six months of that study really weren't enough to warrant six months. If I had to do it over again maybe I'd do it differently, but at the last minute we were in Belgium, Brussels. I came up with a bunch of studies that I thought – I was building this database retrospective, that to me made it look like, "Wow, the six months were important." So just before -- up to that point, we were going to go along with the six months, with the Europeans, when we harmonized on six months. Then I found some data that changed my mind. So I found the data that changed my mind. So when I got up to talk in Brussels, I said we didn't agree and everybody had assumed we would agree by then. So oh god, that was really something. You know, it's like somebody getting up and saying the opposite of what everybody expected you to say. Oh god.

Shostak: And then you know there's going to be a long debate.

Contrera: I didn't think so. It was just my viewpoint, and scientifically I couldn't say six months because I had information to the contrary, and I thought this was a scientific -- you know, it was like a scientific organization. But it's more than that. Science is only 30 percent or 40 percent. The political power -- there were agreements, and then there were quid pro quos and then there were all kinds of things that I didn't realize, that before you did something like that you had to negotiate those things, and no surprises like this. You don't do things like that. I've learned since then, but -- oh it was bad, and it's never been solved to anybody's satisfaction. I think we compromised on nine months.

Shostak: Has the WHO or IARC had a role in or a response to the ICH guidelines on transgenics?

Contrera: Yeah, the World Health Organization were observers. They sent some people. They don't contribute or are not involved in the negotiations or anything of that sort. And I don't know where IARC fits in [unintelligible] observers.

Shostak: Okay. But they didn't have any objections?

Contrera: No. Well, I don't know about that.

Shostak: They were quiet observers.

Contrera: But they had opportunity to comment, and they did and that's about it.

Shostak: One more question, and this isn't a strictly historical question, this is just my own observation and curiosity. Whenever I'm studying a new technology and its use in the regulatory realm, I end up talking to people from CDER, and the same names come up over and over again. And this is true for toxico-genomics, for transgenics, for molecular biomarkers and mechanism-based studies. So CDER itself becomes interesting as a place that is more open to innovation, more oriented towards new technologies.

Contrera: Yeah.

Shostak: I'd just be interested in what your thoughts are on how it is that that's become the case.

Contrera: I'm not sure. Well, I think -- it's hard to say. Probably a lot of that is involved in there's a certain tradition that's developed over the last – I think it's been here, but certainly the last generation that it's developed. Partly personalities…a little more openness to innovation, I think partly driven by the products themselves that human drug therapeutics, the most competitive area, the pharma counterparts, fairly strong, scientifically motivated, and there's more interaction between pharma scientists and CDER scientists. We have twice-a-year meetings with them on scientific issues that they bring up and that we agree to, so that we have a pharm-tox -- they have what they call their Drug Safety Committee, DRUSAFE, it's called, and we have, I think twice a year DRUSAFE meetings. In other words, they bring up issues, scientific issues that they want to discuss with us. So there's a lot of that activity. They're actively involved in nudging us to a great extent, and that's part of it. And it may be the nature of the drugs and the business, but also I think we've had a research group here that was involved in trying to keep up, a laboratory group when Frank Sistare was here, and that I think we realized that there needs to be some place for innovation and we can't wait for academia or for industry to develop these technologies, that the agency has to play a really active role in it for our own good, or else it may dominate us. We won't be in control of it to a great extent, we'll be ignorant of it, to try and keep up with what's going on in industry and in genomics and in all kinds of areas, rather than be passive and be dragged along -- keep up, you know. It's not easy to do because we have a very small group and it's not like it's huge. But it's more the orientation. There's probably not any -- I mean, CFSAN probably has as big a group or bigger group, but for some reason we've taken more of a leadership role than anybody else has. And it might also be -- I think it has a lot to do with our leaders. I think with our Center director, who I think is oriented -- Janet Woodcock and people that she has are more open-minded and more oriented towards looking for better ways, quicker ways and better ways of getting things done. I think that, whereas -- again, my own personal view, from the other Centers, is they are rather kind of – things are pretty much set in stone and more comfortable with – and it's easy to just do things the way you've always done them; it really is easier, you know. You just go along, you got your red book and you check the boxes and everything; "It can't be better than it is now." Trying to change things is not easy. But I think that the Center, I think that has taken a leadership role. We've got clinical people in terms of clinical design, I think leadership roles, and so the quality people we took. Manufacturing -- a lot of innovation coming out of there now to trying to streamline the way things are done. So I think the Center has a tradition in that, you know. Not that they spent a huge amount of research, but they do have a traditional core. And pharma, I think, stokes it too.

Shostak: Right. And it's interesting, because it seems like in the case of transgenics you stoked pharma.

Contrera: Yeah, yeah. We played --

Shostak: So it goes both ways.

Contrera: But we had counterparts that were good friends of ours, you know, but they were -- at least there was an honest interaction, a constructive interaction between us, where they actually contributed and not only just critical, but somewhat constructive criticism. Certainly paying to have studies done -- I mean, when you actually open your wallet, I mean, that's real commitment. [laughs] So it's just talk.

Shostak: Is there anything I should have asked you that I haven't? Are there pieces of the story we haven't touched on?

Contrera: No, I guess not. We hope it -- the momentum carries through with newer models at NIEHS or anywhere else, but I think they're probably still the key focus. Maybe that program gets expanded. Who knows? But I don't know what new models we could think of, but I think what we have now is functional, but I'd like to think of it as just as the first generation and better things coming. But I don't know how long that'll be. But it couldn't have been done without them because we wouldn't have been able to make an alternative. There weren't any. [laughs] We probably would have been one study.

Shostak: Thank you so much for talking to me at such length. You're very generous with your time.

Contrera: Well, I hope I didn't bore you.

Shostak: No, I love this project!

Contrera: Oh okay, good. What's the end product?

Shostak: I'll turn this off.

End of Interview