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A Brief History of Risk Assessment

Peter Barton Hutt, Esq., FDA General Counsel

November 1, 2000

TAPE 1, SIDE A

Good morning, everyone. I very much wish that I could be with us at the seminar this morning, but, unfortunately, I have a prior commitment on the West Coast, and thus this videotape appearance will have to substitute. But I am pleased that I can at least fill you in on some of the development of quantitative risk assessment over the past 30 years at the Food and Drug Administration.

But first you must understand that no regulatory policy simply springs full-blown from the head of a regulatory agency without prior history and prior development. And quantitative risk assessment is indeed one of the oldest concepts in human history.

If you go back in history, you find that for centuries, literally from the beginning of recorded history, every recorded civilization has regulated food and drugs one way or another, through laws, regulations, tradition, from biblical times, indeed from the clay tablets of ancient Sumaria to the present. And when you
try to regulate, one of the issues is, how do you define safety.

Let me give you, for example, one of my favorite statutes enacted by Parliament in 1266. The statute prohibited the addition of any substance to the then-staple food supply if that substance was -- and I give you a direct quote -- “not wholesome for man’s body.” Now, that is no different than our current definition of safety, but it provides no operational content. And thus from the beginning of time to today, the whole search in regulatory law is to provide good science that will in fact incorporate an operational definition of safety.

In those days, of course, in 1266 and, indeed, going back to early recorded history, how did we find what was safe? By having either wild animals or domesticated animals or even humans eat the substance. And if you think that’s far-fetched, and if you think that’s ancient history, let me give you just something that happened a hundred years ago.

In 1902 to 1904, the famous FDA Commissioner, Dr. Harvey W. Wiley, wanted to publicize the issue of food safety, and he chose a way to do that that I’m sure you are all going to be somewhat amused by. What he did was find the 10 youngest members of the then Center -- it really
wasn’t a Center, it was a Division of Chemistry in the United States Department of Agriculture, and he took the five leading food preservatives of that time and fed them to those people for two years, a human feeding experiment. There was no concept of animal testing in those days. And to further illustrate just how remarkable this was, one of those preservatives was formaldehyde. So we have, just a hundred years ago, a human feeding study in formaldehyde. That was the way because there was no operational definition of safety that things were determined either to be harmful or to be safe in those days, not that long ago.

Now, things began to change very rapidly. For reasons that are lost in history, suddenly scientists, academic scientists, throughout the country began to develop inbred colonies of test animals. By 1920, animal testing had suddenly come into vogue, and it was, some people hypothesize, largely a rediscovery of Mendel’s laws of heredity that resulted in this scientific progress. But we begin to see in 1920, and going on up through the decades, increased reliance in our country and throughout the world on use of animal testing experiments to determine safety. But the issue remained, what was the definition, the operational definition, of safety that came out of those experiments?
In the 1930s, people began to think about an operational definition, and indeed, there’s a wonderful paper in 1935 by Dr. Berenblum in which he began to focus on the issue of chemical potency. And, of course, everyone knew at that time, that has often been said, that dose makes the poison, but no one knew where to draw the line between a poison and a safe dose. Berenblum was the first person in the area of carcinogenicity that I have been able to find who attacked that on a mathematical basis and tried to resolve it.

But then came along, as it often does in history, a remarkable event no one could have predicted that suddenly began to focus people on the real issue of operational definitions of safety.

In the fall of 1937, a well-known pharmaceutical company of that era, still with us today, Massengill, brought out what today we would call a breakthrough drug, elixir sulfanilamide. The scientific progress that this represented was that sulfa had never before been put into solution, and Massengill solved that problem. They did some chemical testing, no animal testing, rushed this product out into the market, and managed to kill 120 people in two days, because the solvent they used was diethylene glycol. Now, of course, this led to not only a nationwide
recall, but it also led to the enactment of our current Federal Food, Drug and Cosmetic Act of 1938. He was involved in.

But there were two brilliant and really thoughtful FDA scientists who said, “Let’s learn from this. How often do you have this kind of a tragedy that you can turn into a real benefit to public health?” And so Dr. H.O. Calvary and Dr. Hogarth Fitzhugh, FDA toxicologists, both went out and did a remarkable set of experiments. The first thing they did was they collected all the information on the people who had taken elixir sulfanilamide, the dose they had taken, the amount of time they had taken it, and their body weight, and then they figured out who lived and who died.

Following that -- and you can imagine, that’s obtaining an LD50, a human LD50 for elixir sulfanilamide.

Then what they did was go back and do the animal experiments that Massengill should have done. They did them in a wide variety of species: rats and mice and hamsters and dogs, and everything else. And what they discovered was that there was roughly a tenfold variation among humans and roughly a tenfold variation among the animals. They multiplied 10 times 10, arrived at 100, of
course, and therein lies the history of the famous FDA 100-to-1 safety factor.

You will be interested to know that I have never seen this written up. Someday I am going to write up this story.

I interviewed Hogarth Fitzhugh before he died, as well as all the other then-living FDA toxicologists of that era, and discovered that this was one of the great unknown heroic stories of the Food and Drug Administration of that era.

Well, you might say, okay, we have a 100-to-1 safety factor for acute toxicity. What about chronic toxicity? And, more important, what about carcinogenicity?

Fitzhugh told me that all of the folklore I had learned, that the 100-to-1 safety factor had initially been applied to carcinogens, then they had increased it to 2,000-to-1, and then 5,000-to-1, was all nonsense. It was untrue. FDA never once applied a safety factor to a carcinogen. And, in fact, I went back and discovered, as early as 1945, FDA banned its first carcinogen, a substance called butter yellow. In 1950, FDA banned two non-nutritive sweeteners. You probably have never heard of them before: dulcin and P4000. And, thus, long before Mr. Delaney invented his famous Delaney Anti-Cancer Clause and
put it in the Federal Food, Drug and Cosmetic Act of 1958, FDA had adopted a policy of zero tolerance, no permitted amount of carcinogen in any food in the United States could be had. 

Now, this was, of course, incorporated into the law. But the Delaney Clause, I have always thought, was misunderstood. The Delaney Clause does not say that Congress knew that one molecule of any carcinogen would cause human cancer. What the Delaney Clause said was basically the same thing that Fitzhugh and Calvary and the others were saying much earlier, 15 years earlier, and that is, we don’t know how much of a substance is needed. We don’t know how potency plays in the area of carcinogenicity. And, therefore, we will, until we learn more, adopt a policy. We won’t add carcinogens to the food supply. It was a principle of conservatism. It was not based on scientific knowledge; it was based on the lack of scientific knowledge.

Now, only four years after the Delaney Clause was enacted as part of the Food Additives Amendment of 1958, Congress was presented, surprisingly, with quite a different issue, and one that, for our purposes this morning, is very important. Congress had to face this. Part of the food-additives definition excludes from the
definition of food additive any substance that had been approved by FDA or USDA prior to 1958. Included in those substances was a well-known chemical, you all know it very well, diethylstilbestrol, or DES. And what happened was that the largest manufacturer of DES in the country had a prior sanction for that substance. His plant burned down. He built another plant across the street to make the same substance, and FDA took the position that he couldn’t make it because the prior sanction only applied to the first plant and did not apply to the second plant. So, surprisingly, Congress enacted a law as an exception to the Delaney Clause, saying that FDA could approve a carcinogenic animal drug if in fact the residues of that animal drug were not found in the food produced by the animal using methods of analysis approved by the Food and Drug Administration. That basically is what that amendment stated. And, as we will see in one moment, it was that amendment that led to the development of quantitative risk assessment as a regulatory tool in this country.

Now, FDA, faced in 1962 with this amendment, had to come up with a definition of what method of analysis is approved, and what they did was they came up with a mouse uterine acid sensitive to two parts per billion. So from 1962 to 1972, FDA allowed DES to be used, to be made and to
be used in food-producing animals, both in the feed and in implants, based on the mouse uterine acid.

Well, in 1971, unfortunately, just at the time that I arrived at FDA as Chief Counsel, things began to change, and ominous clouds gathered over this entire enterprise. There were three congressional hearings in 1971 questioning FDA’s policy on DES. And USDA decided they would definitively resolve this matter. They later, I might add, regretted that decision very much.

So in early 1972, USDA undertook a study in which they tagged, did radioactive tagging of DES to find out exactly what happened to it in the food, in the cattle that it was used in. And, not surprising -- I’ll never forget it -- July 28th, 1972, I got a telephone call that in effect said, “Not only have we found it, we found it everywhere. We know exactly where the DES is going. It doesn’t get out of the animal. It’s still there, at very low levels, but it’s there.” I spent the next three days writing a Federal Register notice that banned DES from animal feed, and a year later, of course, we did the same thing with implants.

Now, it was one thing to lose DES. The Secretary of Agriculture informed me I had just raised the price of beef seven cents. I must admit, that did not concern me. What did concern me was, we had been approving carcinogenic
animal drugs for 10 years based on this concept of what I came to call, to the consternation of scientists throughout the country, hide-and-go-seek toxicology, i.e., if you can’t find it, it isn’t there. We all know that’s not true. If you can’t find it, it’s because you don’t have good enough analytical methods to find it. That is true.

So I said to the Center for Veterinary Medicine, I sent them a memorandum shortly after the DES controversy abated, and I said, “I will approve no more animal drugs that are carcinogenic based on the old policy. We must come up with a new policy that is both legally and scientifically sound.”

Now, you might say, “Well, who cares what the General Counsel says about animal drugs?” The answer was, since they all, all the approvals had to be published in the Federal Register, they could only get there if I approved them. And since I declined to approve them, there was a growing stack on the right-hand side of my desk of Federal Register notices that, as far as I was concerned, would never see the light of day unless and until we came up with a new method of approaching this. So there was, in a sense, a mounting crisis both in the Bureau of Veterinary Medicine as well as in my own mind.
During this entire time, during this saga of DES, things were going on that, frankly, I had no knowledge about, both in the Center of Veterinary Medicine as well as in academia. People had been trying to confront, on a purely academic level, this issue that Berenblum had started with in 1935. And this culminated in the National Institutes of Health (NIH) in two well-known and well-respected scientists, Mantel and Bryan, coming up in 1961 with a concept that not only quantified carcinogenic risk, but purported to determine what was, in their terms, a virtually safe dose. And they did it by a mathematical model, but they chose as the virtually safe dose a, if you will, safety factor of no greater than 1-in-10-billion risk, $10^{-8}$. That was in the scientific literature for 10 years. And, of course, because it was an academic issue, no one in FDA paid any attention to it at all, except for one person, Adrian Gross, an FDA toxicologist.

Now, Adrian Gross at that time was at FDA. Later -- in fact, he was in the Bureau of Veterinary Medicine. Later, he went to the Environmental Protection Agency (EPA). EPA. He was a difficult person. He was personally not the easiest individual in the world to get along with. He was highly persistent, he was a very, very strong consumer advocate, but he was also a very intelligent and
thoughtful person. And as early as 1970, Adrian had published an article applying the Mantel-Bryan, not to a carcinogen, to a chemical that he thought, erroneously as it turned out, was a reproductive toxicant, the flavoring substance methyl salicylate.

Well, Adrian, in 1971, internally in the Center, or then, as it was, Bureau of Veterinary Medicine, began to write memoranda that I discovered literally 10 years later by reading congressional hearings, stating that Mantel-Bryan ought to be used on substances like DES. Those internal memoranda never got out of the Bureau, never got to me, never got to the Commissioner’s office, and, thus, we were unaware of it.

But when those applications began to pile up on my desk, one afternoon a very, very fine, bright, extraordinary scientist from the Bureau of Veterinary Medicine walked into my office, his name Dick Layman [sp.] -- he’s retired from FDA now -- and he sat down and said, “Peter, I’ve got to talk to you. Here is a possible way to solve this problem.” In less than a half hour, Dick laid out to me the concept of Mantel-Bryan, the concept of a quantified risk, and the solution to the problem. It took me probably five minutes to realize this was in fact the solution, not a perfect solution, but this was the only way
to go, to quantify risk and then determine what level of
risk is acceptable to our society.

That night I called Charlie Edwards, the Commissioner
of FDA, and said, “Charlie, this is the way to go.”

And Charlie, being the person he was, said, “We go
with it.” That decision was made in a matter of minutes.

Nonetheless, it took more than a year to draft this up
for purposes of the Federal Register.

You’ll be amused to know that almost everybody in FDA
found objections to it. Now, why was that? Well, the
Bureau of Foods opposed it because Leo Friedman, the great
toxicologist that he was, and Al Copey [sp.] both said, “We
want to rely on scientific judgment. We don’t want to be
hemmed in by rules and mathematical formula and specific
levels of acceptable risk. Charlie and I simply said, “You
can’t go that way.”

Then the Bureau of Veterinary Medicine weighed in, Dr.
Van Houweling and others there, who said, “We can’t meet
this standard of $10^{-8}$. That would mean that almost all of
these carcinogenic animal drugs would not survive.”

Now, let me explain exactly why they were concerned.
The way that Mantel-Bryan was proposed to be used was as
follows: What you did was calculate the amount of residue
in the food that would be permitted in order to assure only
a $10^{-8}$ risk, and then you require the applicant to come up with a method of analysis sensitive to that level that represented $10^{-8}$. Once you did that, and then you showed no residue at that level, it was approvable.

Now, Van Houweling kept saying to me -- and we came to call this the Sensitivity of the Method proposal -- that the SOM proposal was unworkable. Simply, it was a lovely academic idea, but, in fact, what it would do is ban everything. Well, we now know that it hasn’t banned everything. It is still the policy that is pursued by FDA today in approving carcinogenic animal drugs.

Now, events that we could not have foreseen way back in 1972, when I was dealing with this, have now made this policy, the concept of using quantitative risk assessment, far more effaceable an any of us ever could have imagined.

As you know, and as we all know now, almost 30 years later, many, many more chemicals have been tested and, for example, in the National Toxicology program (NTP) NTP program, 50 percent of the tested chemicals have turned out to be carcinogenic. The improvements in analytical methodology means that we can find these substances everywhere, absolutely everywhere. As early as 1979, FDA actually published a statement in the Federal Register saying that, in fact, every bit of food in the country
contains some carcinogen of one form or another. We could not live without eating substances that have been tested and found to be carcinogenic in test animals. And thus, the old policy that Olgarth Fitzhugh followed in 1945 and thereabouts of banning every carcinogen, we can’t do, and we haven’t been able to do it for 30 years.

Thus, as it turns out -- and none of us, I can tell you, certainly not me, and I drafted much of it, none of us at the time anticipated it would become as pervasive in the entire government and as important to FDA as it, in fact, has become.

There are a couple of other principles we developed at the same time. One of them is that we realized that not everything that came up carcinogenic in a test animals was in fact appropriately designated a carcinogen. And we began to take into account whether in fact the animal was a good model for the human. And these are well-known examples. The most amusing to me is, if you feed calcium to bulls, they get cancer. That has never driven FDA to ban or restrict calcium in our diet. As you well know, BHA and BHT are suspect carcinogens, but FDA has done nothing because they have concluded that the animal model is not a useful model for the human.
A second area where FDA has taken action is to recognize that some carcinogens act through a secondary rather than a primary method. And, in fact, I wrote the regulations back in the 1970s that said that FDA would not ban alcoholic beverages — that was an easy one; I had little doubt about that one — or selenium because they were carcinogens, indeed, human carcinogens, but they acted through a secondary mechanism of action and thus were not under the Delaney Clause.

And, finally, we realized, though, that those ways of getting substances out from under Delaney were [unclear]. The basic mechanism, the basic policy that we had to rely on, had to do with quantitative risk assessment.

What we then saw was the proliferation of quantitative risk assessment throughout the entire food and drug area. For example, the hair dyes 4-MMPD and lead acetate were approved by FDA based on quantitative risk assessment. Food contaminants like aflatoxin and dioxin were approved, or not approved but at least permitted based on quantitative risk assessment. Acrylonitrile and vinyl chloride was recognized to be permitted in food packaging based on these principles, and, of course, other food constituents.
FDA had to go in through this piecemeal, finally came to a food-constituents policy, which states that if there is a constituent in food that is carcinogenic -- and there are hundreds of them -- they are not required to be banned as long as they do not present a significant carcinogenic risk.

The final part of this is, what is an acceptable level of safety? Now, Mantel and Bryan started at $10^{-8}$, 1 in 10 million, and -- I’m sorry, 1 in 100 million. And after considering that and listening to both the industry and to the scientists in FDA, the final regulation on sensitivity of the method and the level chosen by FDA ever since there was reduced to 1 in a million, so that this is a much more realistic risk.

Now, FDA has not only reduced it to 1 in a million, but FDA has flatly said, in probably 50 different Federal Register notices, that the 1-in-a-million risk, $10^{-6}$, means no carcinogenic risk at all, that while that is a mathematical possibility, it is not a real risk in the actual practical world. Moreover, my feeling is that, in the future, there are possibilities for reducing that. Under Proposition 65, for example, California has gone to 1 in 100,000.
Now, where can we reduce that? We can reduce that with better science. If we can understand better the pathways, the mechanism of action of some of these carcinogens, we can understand how animal and humans are either the same or different in particular chemicals or for classes of chemicals. We will be able to have greater confidence in extrapolation from high dose to low dose, and therefore will be able to reduce the 1 in a million not only down to 1 in 100,000, but in some chemicals, much lower than that. I don’t know if we’ll ever get to the same level that we started with Calvary and Fitzhugh of 100 to 1 for acute risk, but certainly we will get below 1 in a million.

What we need most of all in this area is public education. The public doesn’t understand this at all. They hear the word cancer or carcinogen and they freak out. I don’t blame them. It’s a frightening thought. We need to educate people about risk assessment. We need to educate them about the enormous amount of conservatism built into our present system.

There are still consumer activists out there who want to ban every single carcinogen that exists. Fortunately, FDA has never felt that way, they know it’s not possible, and they are willing to rely on good science.
Well, I simply want to close by saying it’s been a pleasure this morning to be able to be with you, even if by videotape. I hope this bit of history is of interest to you and that it will, in a sense, pave the way for the real experts, the scientists, my good friends from Environ, who are going to go into the details of quantitative risk assessment in just a few minutes.

Thank you very much for being with me and for allowing me to be with you.