History

of the

U.S. Food and Drug Administration

Interviewee: Robert A. Eshelman

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

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Interview with Robert A. Eshelman

December 14, 2007

TAPE 1, SIDE A

RT: This is another in the series of FDA oral history interviews. Today, December 14, 2007, the interview is being held with Robert A. Eshelman, who is the CSO GS-14 leading expert on misbranding and new drug matters for selected OTC drugs and other issues in the Division of New Drugs and Labeling Compliance, Office of Compliance, Center for Drug Evaluation and Research here in Rockville, Maryland. The interview is being conducted by Dr. John Swann and Bob Tucker of the FDA History Office.

Bob, we would like to begin with your earlier history regarding where you were educated, both elementary and college, and then move to your career with the agency.

RAE: Okay.

I was born and raised in the state of Washington, where I got my education. I grew up on a farm in a little town called Centerville, Washington. That's where I went through my grade-school years and graduated from high school in a town called Goldendale, Washington. And subsequent to that, I went to college at Washington State University in 1962. I majored in, I think they called it at that time bacteriology and public health -- we call it microbiology now -- and earned a B.S. degree in 1966.

In my senior year at college, I started looking at job opportunities posted at the college. I saw that the Food and Drug Administration was looking for microbiologists, so

I interviewed at the college. An FDA representative came from Seattle to interview me, and I was later offered a job as a microbiologist in the Seattle District Laboratory, which I accepted, and began work there in June of 1966 as a microbiologist in the laboratory.

RT: Do you recall who the FDA recruiter was?

RAE: Jim Burnett, I believe. He was a chemist in the laboratory in Seattle. He came over and interviewed me.

JS: Did you have any sense of FDA at the time or know much about it? Was it the mission of the agency that interested you, or did it just look like a good job?

RAE: At first I wouldn't say that I had thought much about FDA. I knew about it. I remembered the "cranberry scare," of the late 1950s, so I knew about FDA from that standpoint. But when I was looking for jobs, I wasn't particularly looking for any one in particular. I wasn't even looking for a government job per se. But when I saw that there was a position for a microbiologist in the Food and Drug Administration, I thought that sounded like a very interesting job, and so I interviewed with them. But there was no preconceived idea that I would go into the FDA, no.

RT: So you entered FDA service at Seattle?

RAE: Correct.

RT: Do you happen to recall who was the District Director then, just to put it in the context of time? You might not, and that's okay.

RAE: Kenneth . . .

RT: Monfore?

RAE: Monfore, yes.

JS: I suspect you probably did not have too much interaction with him when you were there, at least in the beginning.

RAE: No. And he wasn't there very long; he retired soon after I began working in Seattle. And I don't recall who took his place. Dr. [Charles] Steers was the Chief Chemist. I worked directly with him. He ultimately went to St. Louis Labs shortly after I arrived in Seattle. But, no, I didn't have much interaction with Mr. Monfore. As a GS-5 microbiologist, the District Director was not somebody I directly worked with.

RT: Well, I asked primarily to put it in a time frame for those who might remember the district manager at that time.

JS: What do you recall about the training you received when you started in FDA? Did they just put you in front of a bench, or was it a little bit more involved than that?

RAE: It was a combination. When I first started there, Charles Thayer was the supervisory microbiologist, and there was one other bench microbiologist. They would both go through the procedures with me and explain the analytical procedures the agency had established for analyzing foods and drugs, but primarily foods at that point in Seattle. After about three months, they sent me back to Washington, D.C., for a three-week training course in the Division of Microbiology. That was one of the more formal aspects of the training they had set up for the microbiologists. And throughout time in the lab, they would send me to different training courses that they would set up in the Division of Microbiology. I was also sent to courses at CDC [Centers for Disease Control and Prevention] in Atlanta and at the Cincinnati center where they trained microbiologists. We had formal training in that regard throughout the time I was in the laboratory.

RT: As a microbiologist, your orientation, of course, was primarily to science and the laboratory. In your training, did you ever get to the field to see what that staff did?

RAE: Do you mean the investigation of manufacturing plants?

RT: Yes.

RAE: Microbiologists would occasionally accompany investigators to different plants when they were looking for microbiology contamination issues.

One of the major investigations I participated in occurred in 1967. There was a major problem in Alaska salmon canneries. There were significant problems with their cans not being properly sealed, and so there was bacterial contamination of the canned salmon. The FDA did a major investigation of the industry. Many investigators and microbiologists went to Alaska to inspect the salmon canneries. I spent three weeks on cannery inspections in Alaska.

RT: Was that problem attributable to closure of cans or to inadequate retorting?

RAE: Probably a combination. The one issue that comes to mind more is the improper closure of cans. We'd do can-seam analysis and find that they weren't properly folded over. Again, a lot of these canneries were in remote areas, so maybe they weren't doing quite the quality control that they should. There were cases where the investigators flew out into the Bering Sea to a ship that was processing the salmon. It is quite possible that those firms didn't have sufficient quality control of the processes.

JS: How did we find out about this? Were there adverse events associated, or just through analysis of samples taken?

RAE: To the best of my recall, a lot of canned salmon was shipped to Seattle to

warehouse, and they were discovering that the cans were swelling and exploding, that type of thing. The fear, of course, was botulism, but I don't recall that we ever really found botulism per se with the salmon. But there was certainly a processing problem.

RT: Did you have any consumer complaints, that is, receive any consumer complaints about this industry or this product?

RAE: At that time? I don't recall whether it was consumer or whether the industry itself and the warehouses were finding a problem -- I just don't recall.

RT: Probably the latter, I suspect, at that time because we didn't have a sophisticated adverse reaction to foods or drugs.

JS: Well, did you do drug work as well in this period when you were in the Seattle District.

RAE: A little bit in Seattle, more in Los Angeles.

I did inspect a drug plant in Portland, Oregon, to determine if they were manufacturing sterile products properly and to determine whether they were taking proper care to be sure that they were doing sterile fill.

Most inspections I did in Seattle District were food related because Seattle didn't have a large drug industry at that time.

RT: Would the agency have done any prosecutions or sought injunctions on the salmon problem?

RAE: I don't recall whether there were actually any, because it worked with the . . .

RT: National Marine Fisheries Service?

RAE: Yes, or whatever it was called at the time, because I know we were even up there working with them on the inspections. And I don't recall if there were any prosecutions. There may have been recalls. I'm sure there were recalls because of the fact that cans were exploding, but I don't have any specific examples.

RT: Apparently, the problem was somewhat ubiquitous in the industry up there.

RAE: Yes, it appeared to be fairly widespread.

Again, one of the things I know, of course, I wasn't that experienced in how the regular industry in canning did, but they would ship their cans smashed flat because shipping was an issue to get into Alaska. Because space was limited, you wanted to put as much into one area as possible. So the can would be flattened, and when you rounded it back up, you would have a little ridge there, and a lot of times that's where you'd find they couldn't seal it properly around the little ridge. I don't know if it still is done that

way, but that was the way it was back in the late ‘60s. It would create problems for them to reform the can properly.

JS: Fascinating. I wouldn’t have thought that sort of thing would be necessary, but shipping was expensive.

RAE: It was a long distance to ship, and they did that to reduce the size of the shipping container.

JS: Well, you were in Seattle for two years, and then you moved down to the Los Angeles District office, again in the position of microbiologist. How did that come about?

RAE: That’s kind of an interesting story.

This was in the spring of ’68, I guess. They were overstaffed in Seattle, and at this time the fiscal year was July 1 to July 1, and so they really wanted to reduce the staff if they could by July 1, 1968. Los Angeles needed a microbiologist, and so they asked if I’d be willing to go. At that time, I hadn’t been out of the Pacific Northwest. I thought it would be a very interesting change in career, so I agreed to do that, to transfer down to Los Angeles.

At the same time, another microbiologist transferred out of Seattle to another position, and about 30 days after we were gone, they hired three new microbiologists because they were allotted more positions in the new fiscal year. It’s just the way it

worked. In the new fiscal year, they were able to get more employees, so two of us had left because they were overstaffed in the previous fiscal year, and then they rehired three to backfill in the new year. There was no pressure for me to go. I just felt that it was a good career opportunity. To me, it was one of the best things that happened in my career.

JS: Did the promotion come at the time you moved, or was that later?

RAE: Not immediately. I think it was because I wasn't quite eligible. It came shortly thereafter.

RT: Now, probably at Los Angeles, you got into some different fields or different industries than salmon. Were any of those notable in your recollection?

RAE: In the analytical side in particular at that time, we would analyze drugs for sterility testing. Soon after I arrived in L.A., I believe it was Abbott that had a major problem with the large-volume parenteral sterility issues. We got into a large program of analyzing parenterals for sterility and did find those that were contaminated. And, as I recall, it was a major GMP [Good Manufacturing Practices] issue; that would be whether the cooling water wasn't properly handled or whatever, but there was a major problem at Abbott, so we got involved in that. I wasn't involved in any investigational aspect at the firm – just the analytical aspect of finished products.

RT: A lot of Abbott's production is in the Midwest. Was there also an Abbott facility in California?

RAE: I don't recall a facility there or whether they would just collect samples at local distribution spots. I don't recall. Baxter McGraw was one of the major ones, I believe, in California at the time, but I don't recall whether Abbott had facilities out there.

JS: But I gather, if I'm hearing you right, that once the problem with Abbott cropped up, we started to look at not just their large-volume parenterals, but maybe take a larger sweep?

RAE: I know we analyzed products from other sources. I don't know what part of the program it was, but I'm sure that they did look at others because it was such a major problem with Abbott's processing, that is, a GMP issue primarily, as I recall.

After a few years, they consolidated the sterility testing in other labs, so we didn't do sterility analysis there after a few years.

RT: Who was your lab Director in Los Angeles, when you went there?

RAE: John Weatherwax.

RT: Oh, yes.

RAE: And Gordon Wood was the District Director when I first got there. And then Abe Kleks replaced him.

JS: Gordon Wood liked to collect photographs, a lot of them, because we actually have a lot of those in the FDA History Office collection that Gordon Wood had compiled, so we actually owe a lot to him.

Now, you also got involved in training, training other microbiologists when you were in Los Angeles. What was that like?

RAE: After I had worked in the lab a while, I would help train the new microbiologists that were hired. I would help train them, to make sure that they understood the processes of analyzing the samples. We had manuals on how to test, procedures to go through, so we would make sure that they were familiar with those procedures and did the proper testing. It was basically to train the new people as they came in.

RT: Was that during the period of Project Hire, when we increased our staff notably?

RAE: Actually, in the microbiology area, it was somewhat independent, as I recall, of Project Hire, I think, concentrated more on investigators.

RT: That's true.

RAE: So we got a lot more investigators. We did pick up some microbiologists, but they would come in at different times. As I recall, we hired Herb Hammond as an employee there maybe in late ’69, which was even before Project Hire, and then there were others who came along a little later.

RT: As a person who’s been in the laboratory work at that time, do you think there’s the same ease of transferring people without objection in the laboratory services as in the field investigations?

RAE: I don’t know. Laboratory people, I think, were less likely to transfer. There was the, early on at least, the idea that if you really wanted to advance, you got multi-district experience. And that changed over the years. But it was probably one of the reasons I was willing to transfer, because I realized that this was advantageous to your career. But there were some people who were able to advance without transferring. I recall one compliance officer in Los Angeles who had never transferred out of the District, and I think some people in headquarters were a little surprised when they realized that this person had worked his way up to that level in the same district. In any case, I don’t believe that laboratory people were as likely to transfer as the investigators were.

RT: That was my impression. I just was asking for your verification if it was true.

RAE: Yes.

JS: You mentioned just previously about the role of manuals in the training, and to what extent were the field scientists involved in the construction of these manuals? I imagine to a large extent they came from the headquarters scientists. But was there a role for the field microbiologists and others, other scientists that you know of, in putting together the manuals?

RAE: Yes, there was. I didn't particularly participate myself, but if one of the microbiologists did come up with a new method or a variation on a method -- I think even more the chemists would do this, too -- you could get that method verified and that could become part of the process. Although I'm sure the headquarters people had a lot of input on what went into the manual, but my recollection was that the field microbiologists certainly had input into the analytical procedures and they'd come up with new ideas or improve the tests, and these could get entered in as long as they were verified.

JS: Along the same lines, were you involved or your colleagues involved to much extent with the American Association of Analytical Chemists in the work they did in developing procedures?

RAE: Along that line, I recall more of the chemists, of course, certainly were involved more directly. We would attend the AOAC meetings as microbiologists, and so there would be opportunity there for our lab people to get involved in it. I don't recall whether

my colleagues in L.A. did or did not directly contribute to AOAC methods, but certainly the opportunity would have been there to participate.

JS: Well, one of the things that I found fascinating in the years I've been here is learning how things have changed in the field in terms of the role of science and research in the district office laboratories and how that shifted over the years. And so that's in part why I'm curious about the extent that you and your colleagues had an opportunity or did not have an opportunity to develop research methods or other activities that could sort of fall into that general rubric of research.

RAE: Yes, the opportunity was there to do research. I was not a researcher myself in that regard. I know others were. And at that time one would hear the complaint, "Well, we never have enough time to do research. You've got to do all the mandatory work." But, yes, it was the opportunity to do research projects, and that project could result in a new methodology.

I recall we had one microbiologist in Los Angeles who did a lot of work on fluorescent antibody identification of salmonella, and so we did get a fluorescent microscope for the lab because of that. A fluorescent microscope was not a cheap item, and they were reluctant sometimes to pay that much money, but he was able to convince them that this was a research project he could do. And I don't recall whether he ultimately got an official method out of it, but I do know he did research projects.

JS: He was obviously involved in it, though.

RAE: Yes, definitely.

JS: Did you have a Science Advisor who worked with the laboratory from a local university?

RAE: Yes, Dr. Pickett, from what I remember, out of UCLA would work there. And he would work on projects with our lab personnel.

JS: But Dr. Pickett was also there to assist with, I guess, routine kind of work in case some of the analysts came upon a problem doing an analysis?

RAE: I don't recall exactly beyond the research issues, but if you had questions on routine analyses too, I am sure that he helped with those.

RT: I think at L.A., you got into OTC labeling and safety issues. What drew you to that part of the scientific work?

RAE: I didn't get into OTC drugs particularly in Los Angeles.

RT: Okay.

RAE: That was not until I got back to headquarters. Working in the micro lab, it was

across spectrums, foods, drugs, even occasionally cosmetics, but I wasn't focusing on OTC drugs until I got to headquarters.

RT: Okay.

JS: But this was a major shift for you when the opportunity came up in '74 to come to headquarters and do OTC work. And as I was going through your background information, I just wondered, well, how did this transformation and interest in OTCs in particular come about?

RAE: Well, actually, I didn't come back here to do OTC work. I came back to the Center for Drug Evaluation and Research, which was the Bureau of Drugs at the time.

It was, as you gather, a complete career switch. And one of the reasons was at that time the GS-11 was basically the highest grade you'd get in the laboratory, other than going into management, and I was not really gearing my career toward management. But if you want to get into compliance work in headquarters, you had the potential for going up to, at that time, a GS-13.

So, I viewed it as a career change with a chance for advancement. Also, people in the L.A. office had transferred months before, so I had an idea of what the work was like in drugs compliance, and it sounded interesting to me; it did sound fascinating. Even though I was to leave my basic microbiology area, it sounded like a very interesting opportunity, and so that was why I transferred here to headquarters. I didn't come into the OTC drug area specifically until about five months later.

RT: As you move to discuss the OTC phase of your work, could you give a comparative analysis or comparative statement on the varying factors? You know, prescription drugs have a very defined procedure and research backup from the manufacturer and so on. In OTC products, how much less stringent or how different is it than the prescription area?

RAE: Oh, there's a lot of difference and there are a lot of similarities, and it is changing rapidly.

When I came into the Bureau of Drugs, which is now CDER, I was working in an area that covered all aspects of drug GMPs, and after about four months they set up the OTC drug team, and that's when I became involved in OTC drugs exclusively.

Despite some differences in OTC drugs versus prescription drugs, the law is the same in a lot of aspects. Primarily, most prescription drugs either had NDAs or Abbreviated New Drug Applications [ANDAs] for safety and effectiveness, or at least for safety under the pre-'62 Act. But for OTC drugs, there were very, very few that ever had been approved by the agency under the New Drug Application process. So they were just out there. Although there were regulations covering labeling of OTC drugs, the agency had not evaluated most of them for safety and effectiveness. Often the claims were whatever a firm decided to put on the product. Although there were regulations for OTCs, they were not nearly as stringent as for prescription drugs.

RT: Was there an area in the OTC field for nostrums or quack, unproven benefits? It

sounds like there might have been more of that because of the close attention given to prescription products.

RAE: There were a lot of OTC drugs with unsubstantiated claims out there, some fairly wild. That is why the OTC Drug Review was begun in 1972. The intent of the Review was to establish conditions whereby these OTC drugs are generally recognized as safe and effective and not misbranded. The FDA didn't feel that we had the resources to do individual NDAs for each OTC drug, so they devised the rulemaking process called the OTC Drug Review, which then set up conditions on a class-by-class basis where you could market an OTC drug, and the agency would deem it generally recognized as safe and effective if you meet these established conditions. If you do that, then you don't have to go through the New Drug Application process.

The OTC Drug Review is a three-step process. An outside advisory panel would evaluate the data that is collected -- this was back in the mid- to late 1970s -- and prepare reports of what they deemed to be generally recognized as safe and effective and not misbranded, and also the panel reported on drugs that were not generally recognized as safe and effective. Then the agency would review that report. They would get comments from the public and industry and then prepare a proposed regulation. The proposed regulation states what drugs the FDA believes will be generally recognized as safe and effective and not misbranded. The agency allowed time for additional comments from the public and industry; and then a final rule is published. That final rule is what the industry can follow to market an OTC drug product without FDA approval.

RT: Well, for example, there are the patent medicines of the last century, some of which have continued even to almost the current period. One of those, like Lydia Pinkham's Tonic, or whatever it was called, is a prime example of unsubstantiated label claims that I think FDA has taken legal action against. There was a plethora of those kinds of mislabeled products on the market in the past.

RAE: There were a lot of those, and we published regulations for some of these categories -- aphrodisiacs, baldness remedies -- where we said that there's nothing that's generally recognized as safe and effective for these indications and therefore they're not allowed to be marketed like they're unapproved new drugs., unless they can show they are safe and effective via an approved NDA.

Maybe a little later we'll get into the DSHEA, Dietary Supplement Health and Education Act, which changed a lot of this aspect and allowed more products to come out with claims that we said were not acceptable if marketed as an OTC drug.

JS: We do want to talk about the supplements and the disclaimer on the supplement labeling and so on.

I guess part of how the OTC review is constructed sounds like we borrowed some elements from the Drug Efficacy Study Implementation, at least in the way outside panels were constructed by pharmacological areas to help in FDA's evaluation of these products.

We did an interview with Dr. Richard Crout, who made a point of saying that when Peter Hutt developed this OTC Review during his tenure as Chief Counsel of the agency, this was placed not in the Bureau of Drugs but, rather, in the Office of the Commissioner. And, at least administratively, that's where it came out of. Because of the required expertise, it had to be operated by the Bureau of Drugs people. But did that seem to have any kind of impact on how it was carried out from your standpoint in the Bureau of Drugs?

RAE: That was early on, and I'm not that familiar with the exact administrative setup, and obviously Dr. Crout is very, very familiar with that, I'm sure. Now the office that handles the review of OTC drugs is the Office of Nonprescription Products [formerly the Division of OTC Drug Products]. In my memory, most of the time it's been in the Center for Drug Evaluation and Research. But certainly it's clear that the Commissioner's office had an active role in it early on. We remember they were . . . There was, as I recall, a steering committee that met quite frequently, maybe up to the Commissioner's level, on the OTC Drug Review.

JS: I have to ask, where do we stand today with the OTC Review?

RAE: Basically, the Office of Nonprescription Products would have to give you a breakdown of where we stand, but right now there still are quite a few categories that we don't have final regulations covering them. There are a lot of them that are final regulations, and those provide an enforcement tool. With the final regulation, it's a little

easier to take enforcement action than if there's no final regulation. If affirm markets products that were out there before the OTC Drug Review began, and it's been 35 years, they can continue to market them until the agency really has fully evaluated them through a final rule, unless, of course, the product presents a safety issue. There are some categories that are still awaiting final rule.

RT: How large a group or staff was marshaled to deal with the OTC issues? Was it a small staff, or did you have several staff persons assigned to OTC issues?

RAE: In our office we're only involved in compliance issues, so we don't get involved in setting up the regulations. That's the responsibility of the Office of Nonprescription Products, and I don't know what its size has been over the years. It varied over time depending on resources. It went from Division to Office, back to Division, and then to Office status, but I do not know the number of people in each phase.

But for us in the Office of Compliance, the OTC drugs team has been there as an entity since 1974, and it has gone up and down in numbers. I think we had as many as nine compliance officers at one point, eight or nine. Then we went down about as low as four or five, and right now we're about that level. When I leave, I think there'll be about five compliance officers.

Sometimes it all depends on resources and what the priorities are, whether it goes to the prescription drugs or the OTC drugs, so it's been up and down.

RT: Over time, I suppose the agency has maintained a very active oversight as far as

the prescription drug approval process. Has there been an interest in OTCs in terms of congressional hearings or required field reports?

RAE: Yes, there has. As a matter of fact, I was at a congressional briefing a couple of weeks ago regarding antimicrobial and antibiotic resistance issues. Concerns in those areas flow over into the OTC arena because the antiseptic products, e.g., triclosan ingredient, in OTC products may be contributing to resistance. Also, the OTC pediatric cough-cold issues of safety and effectiveness recently have come to a head. These issues cover both prescription and OTC products. So, yes, there has been congressional interest in the OTC arena.

RT: What do you think has driven more careful attention to cough and other preparations in that category? Has it just been an outgrowth of the Center's expansion, or is there a body of complaints or legislators' interest in the field?

RAE: I can only really speak to this peripherally because I know what's going on in some of the areas but I'm not that directly involved in others. I know that the pediatric cough-cold issues recently were brought more to the forefront because there was a petition by a group in Baltimore, health personnel there, who were concerned about the safety issues and submitted a petition to the agency, which raised the issue to a greater level.

RT: What kind of an interest group was that? Was it a private one?

RAE: Public health officials, I believe.

RT: Okay.

RAE: And if there are more questions as to the exact procedures regarding that petition, the Office of Nonprescription Products would have more details. But the Office of Compliance was involved to follow up on the compliance aspects of the pediatric cough-cold drugs.

RT: Sure.

JS: We are kind of venturing into this last period in your experience here in FDA, and of course we have a lot to cover there, but these oral histories are seen not just by FDA, but probably even more so by outsiders. It might be useful for an outsider to understand how an action is developed by people like yourself here in headquarters in conjunction with district officials when it comes to a problem area regarding OTC drugs. So I wondered if you could walk us through how headquarters and district offices work in tandem in dealing with a problem with an over-the-counter drug, assuming that the process hasn't changed. Maybe it has.

RAE: You're talking about legal actions, then.

JS: Yes.

RAE: The basic process hasn't changed that much. We work directly with the field people on this. There are compliance officers in each district office, and we work with them basically to establish a case for a regulatory action, which at this point could be a warning letter or a seizure or an injunction. We identify the problem. Sometimes the district will identify a problem or find a problem in their investigations. They'll make a recommendation to us that they believe warrants some sort of regulatory action. It's our position to evaluate that recommendation and to determine if the facts support a legal action, is it violative, and also, does it fit into the agency priorities, do we have the resources to go after it? But basically they would submit, say, a warning-letter recommendation, and if we agree with it, we would approve it and then ask that they issue the warning letter to the firm, which sets forth the violations which we believe are actionable.

The firm is given a chance to voluntarily comply, because the warning letter just says we've identified these violations and please tell us what you intend to do about them. If they accept the warning letter and make the changes, basically that ends that aspect of the case because the problem has been solved.

If they refuse to change or decide that they're going to defy us, then the next process could be, and probably would be, potentially a seizure. At this point, we would ask the district office to go out and document available products to seize, document that the product(s) may have been shipped through interstate commerce, and identify the

amounts and whether they're at warehouses or wherever they are and submit that for our evaluation.

If we agree that the facts support the case, then we would send it on to our Office of General Counsel. As part of the process, the seizure recommendation would be sent through ORA, the headquarters field group that also reviews such actions.

For a seizure, though, of course, that then has to go to the Department of Justice for approval. They're the ones who would actually do the seizure.

JS: They have to approve?

RAE: Approve, yes.

JS: The decision to seize the product?

RAE: Right. Because marshals will then go out and seize the products we have included in the seizure.

There's also a process that may be used if the firm is continually violating some aspect of the law. That is the injunctive process. The procedure is similar in some respects -- the district has to establish that there's a violation and the facts to support that case and all the evidence, and we would review it. And if we agree, then we forward that on again to the Office of the Chief Counsel. If they approve the injunction, it goes to the Department of Justice for approval. The injunction, either through a consent decree or by court order, makes the firm comply with the law.

JS: I guess sometimes getting a firm to agree to a consent decree can be a little difficult depending on the lawyer that's advising them, because the consent decrees can be severe. Right?

RAE: Yes. But a lot of them do. It's a negotiation process. But there are also some that ultimately we do have to go to court and go to trial.

JS: When you get those recommendations, to the extent recommendations might come from folks in the field, as you said, you have to make some decisions, sort of an enforcement triage, whatever you want to call it, but I guess not all recommendations are followed through. Is this a rare event when they're not followed through, or does it happen more frequently? I'm just curious to what extent folks in the field and folks in headquarters see eye-to-eye when there's a problem out there.

RAE: That's a difficult question because it varies from time to time because of resource allocations and priorities, and there will be times when the field and headquarters don't see eye-to-eye. And it's understandable because the field people, they're on the frontlines, they're right there, they see all these violations, where headquarters maybe is a little more isolated. And also, headquarters has the advantage of the fact that you see more from different areas, and so you have to figure out which one is the highest priority or higher priority, and where has the agency decided to put their resources.

There was a time when there really was no allocation of resources for OTC drugs because they just didn't have the personnel in the field to do the required work. They had to cut back, and they felt that it was better to concentrate on prescription drugs. And it's hard. You see the violations there. It's very hard to say, well, we're not going to do something about it because we just don't have the resources to do it. And there's a tension between the field and headquarters, but we try as best we can to communicate. We do.

RT: As I recall -- and correct me if I'm mistaken -- reading some information about your career, you also were involved with training of state officials. Is that correct? The lab people, I assume.

RAE: There was a brief time, yes, in Los Angeles. I think it dealt with a local public health issue -- whether the state or local, I don't recall. It was along the same line as training our new employees, but also would train them in the food and drug type of analysis.

I recall also that there was a person from the Department of Agriculture who came in and worked in training regarding the methods that FDA used for analysis.

RT: California is probably one of the more active states in devices and drugs, and that's why I wondered whether FDA had a cooperative effort at all with the state.

RAE: It would be difficult for me to answer that question because in the lab, as a bench

person, you're not quite as aware of cooperative efforts at higher levels. But as far as I know, there was cooperation between the state and FDA.

RT: Some of the states in more recent times have gotten into various kinds of contracts with FDA to perform certain field inspections and so on, including sharing of the regulatory data with the federal agency. I think that in New York they've done some of that too, and cross-authorized FDA to take a regulatory action in lieu of the state, and vice versa, the lacking of state action in lieu of federal action. It's rare, and I don't know how successful it is, but there have been some attempts made along that way.

JS: If you don't mind, I'd like to go ahead to the period of the position that you now occupy and you have since the year 2000 as a peer-review CSO. You're the lead expert for CDER on drug and new drug determinations when it comes to labeling, particularly for cough-cold preparations, dental products, and those dealing with oral health.

You mentioned earlier the impact of the Dietary Supplement Health . . . Am I right, DSHEA, Dietary Supplement . . .

RAE: Health and Education.

JS: Health and Education Act. We rely on an acronym too much in the government, I think.

My guess is there are plenty of products, dietary supplements that are used for coughs and colds and for oral health and so on that you deal with. I guess one sees on the

market so many products that seem to make some claims, yet they are able to do this without going through the formal drug-approval process because there seems to be a statement on the label that what is said on the label isn't necessarily approved or evaluated by FDA. I wondered if you could tell us a little bit about how the situation we have today came about.

RAE: That's a poser, but DSHEA passed in 1994. One of the definitions of a drug is to cure, mitigate, prevent, treat disease, but another one is products (other than food) that alter or affect the structure or function of the body. So products out there that would claim to affect the structure or function of the body, although not a disease claim, it still is a drug under that definition.

Well, DSHEA changed that by saying that dietary supplements could make structure-function claims and not be subject to regulation as a drug. That had a major, major impact to us on the OTC Drug Review because some of these products, such as sleep and weight-loss products, have structure-function claims that's not disease, so they may be marketed as dietary supplements.

Also, the claim for "nervous tension," which we said there are no drug products out there that are generally recognized as safe and effective for daytime sedative use as a drug, well, with dietary supplements, you have the herb that comes out with daytime sedative claims, it comes under Dietary Supplement Health and Education Act. That's a structure-function claim. It's not a drug. So these products that we had said can no longer be marketed as drugs can now come back on the market under DSHEA with no approval. And that statement you mentioned -- it's not been evaluated by the Food and

Drug Administration -- is required by DSHEA to be put on the label. Again, that's more peripherally because, again, CFSAN, Center for Food Safety and Applied Nutrition, has the expertise in this area. But that statement is on there to say that this product has not been evaluated by the Food and Drug Administration.

JS: I guess it certainly leads to the question: How did this come to be, and is there a possibility that we might find other products FDA regulates in which the 1938 law is preempted by putting an exclusion on labels? How did this very fundamental element of the law come to be -- well, looking for the right word here -- come to be avoided or sidestepped with this exclusion?

If you want an opportunity to talk about DSHEA, this is your opportunity, and if not, that's fine too. It's your oral history.

RAE: Well, we all have our own opinions and thoughts on it, but I have to defer on how this came about because I just know what you hear and read in the papers and things like that. You know, the dietary supplement industry was able to get this through Congress and to get these new laws that allowed them to market these products.

And historically, if you look at maybe, with the Food and Drug Administration a lot of times, it goes back to the 1970s, Section 411 of the act, the Proxmire Amendment on Vitamins and Minerals, because people thought the agency was getting too strict on regulating vitamins and minerals. So it all depends on who has the ear of Congress, I guess. I wouldn't speculate on how DSHEA came about, but it just got through

Congress, and therefore just makes it difficult for us or it changes our enforcement approach on a lot of these products because we could no longer call them drugs.

JS: I heard once -- I don't know if this is true -- that in response to our proposed regulation of vitamins and minerals and supplements in the 1970s, the Congress received more mail that was concerned about this action than they received in response to Watergate. I don't know if this is true, but I suppose it wouldn't surprise any of us here in FDA, would it?

RAE: It wouldn't be a surprise, no.

RT: Well, in your role reviewing and evaluating evidence from inspection reports and the like, that took you another step away from laboratory practice itself. Did you enjoy this later phase?

RAE: Yes. It was a totally new career, it really was. There was a lot of information in the microbiology area that was very helpful in terms of starting out in this. But I went from a lab bench job to a desk job, and now it was purely paperwork, reviewing of documents. But I've always been fascinated by the work.

I find the legal aspect, the regulations, can be confusing at times maybe, but it is very interesting to look at the background as to why they got there. So that interested me. And you have to try to figure out, when you're analyzing something, do you want to take an action here, what impact will it have in other areas, and I just found that to be very

interesting. Even though the compliance work is a complete change from my first eight years, I've really enjoyed the entire time.

JS: We're jumping around a little bit here, but I appreciate your bearing with me.

RAE: Fine.

JS: You've served under a number of Center Directors since you've been here. Let me ask you if you can go back and recall if there are elements about them, their leadership, that still rings with your memory of them, if you care to say anything about that.

RAE: Well, you mentioned Dr. Crout, and, of course, he was the Center Director when I arrived, and he was here a few years. We always had a very high respect for him in terms of the OTC drugs arena. He had a good understanding of it and was very sympathetic to our cause, as much as he could be. Sometimes you have priorities otherwise. We always felt that Dr. Crout was supportive of the OTC drug program.

At that point in the late '70s, the OTC Drug Review, as you mentioned earlier, there was a lot of involvement at the Commissioner's level, and so we felt there was a lot of support there. Not to disparage any of the subsequent Center Directors, but priorities changed, and they had to focus their resources elsewhere as they saw fit.

Particularly we noticed a change, or at least in our minds anyway, when PDUFA, the Prescription Drug User Fee Act, was enacted. That became the top priority because

you were under mandates to do this, so we perceived that the priorities, of course, shifted to prescription drugs.

JS: By the way, when the decision is considered to move a prescription drug to OTC status, to what extent, if any, do you or your office get involved in decisions like that, because there have obviously been some major ones in the last five years or so, gastrointestinal and other kinds of products, not necessarily under your specific area of expertise, but I think people often don't understand how decisions like those are made.

RAE: As the compliance group, we are not as involved in that process as others because we are more involved with the follow-up enforcement of any changes.

But to go back to the process of the OTC Drug Review, which included potential switches from Rx to OTC under the OTC Drug Review monograph system under the regulations, that created some problems early on in that panels would make recommendations for product switches from Rx to OTC.

One in particular, chlorpheniramine maleate, the antihistamine, which was 2 mg. OTC and 4 mg. prescription. The panel started deliberation and decided that it should be 4 mg. over-the-counter. Firms looked at the minutes of the panel meeting or they were sitting in on the meeting, and decided to switch products from Rx to OTC right away. And so you had a flurry of this, back in the mid-'70s, products switching from prescription to over-the-counter status without full FDA input. It reached a point where we, in Compliance and others in the agency, worked together to come up with a regulation that in essence says you can't do this, you can't switch until the agency says

you can switch, until we have a regulation out there at least that says you can now go to over-the-counter from prescription status. And that was back in the mid-‘70s, 1976.

Subsequent to that, there were more products that did switch through the regulations, but today, as a practical matter, these Rx-to-over-the-counter switch are prescription drugs that switch through the NDA process rather than going through the monograph system.

And one of the reasons for that which was given -- and it makes a lot of sense to me -- was, particularly then, you did not have to file adverse-event reports on over-the-counter drugs, period, unless they were subject to an Approved New Drug Application. So if you switched through the monograph system, the agency would no longer get any adverse-event reporting, so you wouldn’t know, when this product switched to OTC, whether there were significant adverse events. So that was one of the reasons for relying on the NDA process. If we keep it under an NDA on the OTC, we at least will have the required submission of adverse events. We’ll be able to monitor it a little better than if it went into the monograph.

JS: Okay. I would imagine, as the agency is considering certain cases of an Rx-to-OTC switch, there might be issues, compliance issues, which probably should be taken into account; I’m sure those are taken into account when the decisions are made. I would imagine that would be something experts like yourself would certainly be asked to weigh in on some of those issues.

RAE: We would comment where we felt it was important. Early on, when switches

were going through the monograph system, we would try to see where there might be pitfalls, you know, if this switches, what's going to happen, or is this warning understandable to the consumer. Sometimes it's more difficult if you're used to having a prescription drug and the doctor is used to having control over it, they know what the warnings mean or what they should mean. Well, what does the consumer know about this warning? We maybe need more of a layperson look at it or thought process on whether this product should have this type of warning, or does the warning really seem to work very well.

I think that primarily now, like I said, it's through the NDA process. We do get involved with them, but not to a large extent.

RT: Of course, in the OTC sphere, these preparations are regarded as safe enough for consumer use and administration per the directions. Thus, I assume there's really not any network or volume of adverse reactions coming back . . .

TAPE 1, SIDE B

SIDE B OF TAPE IS BLANK

TAPE 2, SIDE A

RT: We had a change of tapes.

You'll recall kind of what I was asking you about, Robert?

RAE: The adverse events?

JS: Regarding over-the-counter drugs, how can we find out about adverse reactions associated with those that fall outside of the NDA?

RT: That's correct.

RAE: The law keeps changing. That's what makes the job even more fascinating.

A year ago, I think it was December 22nd, a new law was passed that added some requirements for reporting adverse events for over-the-counter drugs subject to the monograph system. And I don't have it right in front of me exactly. It's not the same. Under an NDA, OTC NDA, you have to report any adverse event you receive. The ones that are under the monograph, they will only need to report those that are significant hazards, serious adverse events. They're mandated to start doing it by the end of this month [December 2007].

JS: You're talking about the manufacturer?

RAE: Or distributor will have to, whoever receives the report. A person responsible for the product is responsible for submitting the adverse-event report to the agency. As that just starts this month, I don't know how that will work out. We should be getting more adverse-event reports in because they'll at least be required to submit them. Again, that's

only serious events, not your “it made my head ache” or something similar. That wouldn’t be reported.

RT: Probably there’s a relative dearth of that kind of reaction anyway as compared with the stronger preparations under Rx control.

RAE: One hopes so.

It’s interesting. And, again, I’m not a toxicologist or anything else. But when I started in the OTC drug area, acetaminophen was thought to be one of the more safe ingredients and did not present a problem. Well, now you look at acetaminophen, and it’s probably one of the serious concerns about potential overdose and serious adverse events. So things change over the years. And it’s the same ingredient, so you knew we were having the same problem before, but whether the adverse-event reports wouldn’t be coming in or whatever, now maybe there’s a better adverse-event reporting system. That’s just my thoughts; I mean, I don’t have any data to show that. But we do know there are serious concerns about acetaminophen toxicity, and it’s apparently not that much greater than the therapeutic level.

JS: Do we get much feedback through the MedWatch system in which both consumers and their caregivers can file reports with the agency? Do we get much through that system, like with the OTC products which are under your purview, on which we can make some decisions or actions or what have you about these products?

RAE: I don't have a lot of background in that, but we do peripherally get some reports through MedWatch of adverse events that I see, because they'll ask if it's something that we should be following up on, or we'll just see copies of what's sent to the field. So there are some reports under MedWatch.

There's also a group, I don't know the exact title, but they look at the adverse events, and they'll contact us at times because they see that maybe there are labeling problems which might be associated with problems or which we could correct an adverse event if they changed the labeling. But I really don't have a lot of background in the MedWatch. We have another division that handles those reports, so I really haven't gotten into it.

RT: You mentioned the size of your staff earlier. Is the cadre of employees primarily microbiologists in your OTC review work?

RAE: No. The Consumer Safety Officer position title covers a broader scientific field. You must have 30 hours of science background, but it can be in different areas. We have pharmacists and we have biologists. So there may be some microbiologists, but in the Consumer Safety Officer category, the background is scientific, but it doesn't have to be microbiology.

RT: Were these personnel derived from CSOs that worked in the pharmaceutical arena? Or would you have acquired CSOs at-large who may be former food

investigators? I wondered if there was a specialization ability required for this particular work.

RAE: Early on, most of the CSOs in headquarters had field experience, and a lot of them were investigators. There were also lab people. Then they even started hiring from non-FDA positions, so you have pharmacists who maybe had never worked in the FDA field. But we feel that they can be trained in the law and regulations to understand what is required of these products, so you have people from different backgrounds now than maybe you would have had 35 years ago. You have a broader background in the CSO. When I came back here, most of them had backgrounds in the field, although they were hiring, then, pharmacists who had never been in the field.

RT: It's an ancillary point, but I just thought . . .

RAE: No, it's very interesting because it has changed over the years, because now a lot of people do not have field experience. You know, the practicality of it, it's very expensive to move nowadays, and it's harder to get people to transfer into this area.

RT: Certainly. For example, going out to California is almost like taking a demotion, I have heard.

RAE: Yes.

RT: But you get a better grade or two.

RAE: Yes.

JS: Well, speaking of moves, I have to ask a question of you, and I haven't asked this, and maybe Bob's asked this before, but I haven't. But you're in White Oak now. Is that . . .

RAE: No, not yet.

JS: You're not.

RAE: I'm in Montrose Metro.

JS: Oh, that's right. Okay. I guess I can't ask my question, then, which was going to be, tell me about the move to White Oak and how this was. But I forgot that OC and ORA's Division of Training are both over in that building.

RAE: We moved there five years ago. The Compliance group is moving to White Oak, but I'm not moving to White Oak.

JS: You're not.

RAE: They're moving to White Oak early February, but I will be retired by then.

JS: Okay. I knew just about everybody else, but for the Office of Training and Communications here in the Parklawn Building, they're going to be moving the first, early next year. And, of course, OC is going to be moving as well.

RAE: And Generics and . . .

RT: Well, for folks like myself, as many staff people who come from Virginia, it's a little farther north. It isn't particularly a move of better traffic or commuter convenience.

Well, have we pretty much covered it?

JS: I think we've covered the areas that we wanted to. But, of course, if there's something that we haven't touched on that you think should be here, we certainly want to make sure we address that.

RT: Sure.

RAE: I think it's been enjoyable.

JS: It's been our pleasure. As we mentioned when you were contacted, the area that you've dealt with in your career, some of it overlaps a little bit with some of the other

oral histories, but it's always nice to get different perspectives on what it's like to come to FDA. Everybody has different reasons for coming to the agency and moving around. But the expertise you've developed in headquarters since you arrived here back in the 1970s is an area of expertise that we really haven't been able to tap into for our oral history program, so we do appreciate that.

RAE: Okay.

RT: Thank you very much, Bob.

RAE: Thank you.

END OF INTERVIEW