Exclusive Interview with Dr. Paul Anderson: The FDA and the Fate of Compounded Medicines

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The *Journal of Restorative Medicine* (*JRM*) recently interviewed Paul Anderson, ND, who is testifying at U.S. Food and Drug Administration (FDA) hearings in support of maintaining the availability of several hundred compounded medicines. The FDA is considering enacting legislation that would make it illegal to compound or possess these commonly prescribed natural substances. If enacted, this legislation would affect clinicians as well as compounding pharmacies. *JRM* believes it is crucial for integrative medicine practitioners to have information about this process.

JRM You've been attending hearings at the FDA, where the fate of a large number of natural medicines is under review. Please give us an overview of what's going on and how you came to be present at these hearings.

Dr. Anderson A number of years ago, the FDA asked compounding pharmacies, natural medicine practitioners, and integrative medicine practitioners to nominate substances for a hearing process. I believe the people who nominated substances took the FDA at its word, namely that all substances would get a fair hearing. However, the FDA's motivation was that if any of these substances did not have what is known as a USP-NF federal monograph (a combination of two compendia: the United States Pharmacopeia and the National Formulary), regardless of whether the substance was a regular drug, an off-label drug, or a natural substance, it would become illegal to compound. These hearings are referred to as the "bulk drug substances for pharmacy compounding" under Section 503A of the Federal Food, Drug, and Cosmetic Act. Around 310 substances were nominated for review. The FDA said it would look at each of these substances individually. I've attended the hearings as a subject matter expert. Subject matter experts write testimony that gets included when a substance is nominated for review, as well as attending in person to testify on behalf of that substance.

JRM So, what is happening to the fate of these 310 substances?

Dr. Anderson Contrary to what we expected, the FDA went through the list of 310 substances and said that only a certain number of them *even warranted a hearing*. As a result, the list was cut down from 310 to about 68 substances that were deemed worthy of a hearing. The remaining approximately 242 substances, most of which happen to be natural medicines, got assigned to category 3, comprising bulk drug substances nominated without adequate support. This means that if the FDA process is enacted as a federal rule, these substances will automatically become illegal to compound, without even having had a hearing.

JRM What are examples of some of the substances listed under category 3 that would become illegal to compound?

Dr. Anderson *Lactobacillus acidophilus*, alfalfa, anise seed, certain types of copper, certain types of magnesium, a lot of minerals, a number of herbal substances that might be used in a compounded sense, and a whole host of things nominated by

pharmacists that aren't used as medicine but are used as binders or excipients (such as powdered milk) and would become illegal according to this list for a pharmacy to use. In reality, what it comes down to is everything will automatically be illegal to compound, except whatever tiny fraction of substances of the already small group deemed worthy of hearings that make it to the FDA "yes" list!

JRM What has happened to the remaining 68 or so substances that were deemed worthy of a hearing?

Dr. Anderson Those substances were put on the category 1 list. As of this time, hearings have taken place for 53 of them. Thirty have been deemed unsafe for compounding; 16 have been approved as safe; and about 18 are still awaiting hearings. Examples of things on the category 1 list that did get FDA hearings and which the FDA says should be illegal to compound include many substances that are inside our bodies, such as acetyl carnitine, certain forms of glutamine, chondroitin, D-ribose, and a number of other things that we actually can't live without. The list also includes commonly used natural substances such as artemisinin, *Boswellia*, MSM (methylsulfonylmethane), glycyrrhizin, and certain B vitamins such as nicotinamide. The way the FDA hearings are set up, if these substances do not have some very clear medical indication for which they are the only treatments, the FDA essentially tells the committee that they should not approve it.

JRM And that's a catch-22 for natural medicine providers.

Dr. Anderson Yes, it really is. I'd like to tell you about something that gave me insight into the underlying logic and world view of the FDA with regard to compounding. In my clinical practice, informed by a growing evidence base, we were compounding curcumin, which is now on the FDA "no" list, to use in very high doses with patients who had advanced cancer for which nothing else was working. The results were that progression of metastases stopped in a number of patients and metastases actually regressed in a few. So, this worked as a proof of concept without a single high-grade adverse event. In about 2015, we nominated curcumin to be reviewed by the FDA because it was not an approved drug, and we were trying to ensure it would remain available to patients. Nobody on the FDA panel seemed interested in our findings, though.

Then, a couple of years later, I saw that a patentable synthetic form of curcumin, called Lipocurc™, was in development. It cannot be safely used in anywhere near the dosage that natural curcumin can, but it's patentable because it's a synthetic molecule. It will become a chemotherapy adjunctive drug, but compounding natural curcumin might well become illegal. It does appear that any natural substance shown to offer a glimmer of hope, especially in cancer treatment, will be put on the FDA "no" list, but if a pharmaceutical company wants to develop a drug from it and has enough money to invest in trials, they can go ahead and do so.

JRM It's hard not to interpret it that way.

Dr. Anderson This is not my conjecture. The FDA has actually declared on record in the publicly available *Federal Register* that it does not understand or trust compounding but does trust pharmaceutical companies. The adjudicators on the panels are not bad people; they just firmly believe that the only way to protect the health and safety of Americans is to have the pharmaceutical companies control medicine and to minimize compounding. But at some other level, it's hard not to believe that some strings get pulled by big pharmaceutical companies to make this happen. In one question-and-answer period during the hearings for a particular natural substance, an FDA committee member actually said if this substance was so important, a pharmaceutical company would have made a drug from it.

JRM I've heard that even though the FDA is using the term "compounding," their ruling would affect clinicians as well as pharmacies, meaning it would become illegal for a practitioner to mix ingredients together in their own office for, say, a tincture. Is this an accurate interpretation?

Dr. Anderson Yes, that's a very good point. It's not just pharmacists that the FDA considers to be compounders. About 2 years ago, the rules were changed so that physicians who do anything either nonsterile (e.g. oral substances such as tinctures) or sterile (e.g. injections) have to comply with USP 795 (Pharmaceutical Compounding – Nonsterile Preparations) and USP 797 (Pharmaceutical

Compounding – Sterile Preparations). So, let's say you as a physician put together two, three, or four items on the FDA "no" list into one bottle *in your office* to make a tincture; that is technically compounding. This confuses a lot of practitioners. For one thing, most doctors don't know that they are now considered a compounding pharmacy.

From the clinician's perspective, if we wanted to give a patient a tincture with four ingredients, we'd need to put them in separate bottles and tell the patient to mix them up at home. It would require a lot of effort for the FDA to enforce these rules at a practitioner level, but it opens a door for potential investigations.

Let me just clarify again: The FDA ruling is not enacted yet. Compounding pharmacies can still make any of these things for now. This is confusing, because even if an item is on the "no" list, the FDA has to wait until the end of its process to enact all of these rules. But please remember: A very large list of items is under threat. Here is a link to a list of these items and another link to the same list with annotations that I provided during a Q&A:

FDA list without annotation: https://www.fda.gov/downloads/Drugs/.../PharmacyCompounding/UCM467373.pdf

List with annotation and Q&A: https://www.consultdranderson.com/wp-content/uploads/securepdfs/2018/09/Anderson-Summary-FDA-503-Lists-and-Questions-09-15-2018-1.pdf

JRM What effect would this have on supplement companies?

Dr. Anderson A supplement company would still be allowed to make substances on the category 3 list, because supplement companies fall under a different part of the FDA jurisdiction. But it would become illegal for compounding pharmacies to even possess these substances, in the same way that it's illegal to possess any illegal drug.

JRM By targeting pharmacies first, it's almost like the effect is less directly evident to our patients. It's undermining how we practice, but if the FDA made it impossible for us to practice, it's likely more patients would be up in arms. Patients are a diverse demographic that, in this regard, are more about good medicine and good care than about partisan politics.

Dr. Anderson Exactly. Our patients would eventually figure out that they can't get something from their practitioner that they used to get, and then they will start asking questions. But if the FDA went directly to the public and said, by the way, if you use natural medicines that your ND or integrative medicine MD gets from compounding pharmacies, these medicines will likely be a lot less available come next year, then people might really rise up *en masse*. That's basically what led to the law known as the Dietary Supplement and Nonprescription Drug Consumer Protection Act. That amendment halted the same process that the FDA had initiated only that time for dietary supplements. The major reason why the FDA was not successful then is that the public was tipped off and was able to mobilize strong political alliances in support of keeping dietary supplements available as long as they were safe and didn't make health claims. What's going on currently is a tougher sell to the public, because the majority of people probably don't even know what a compounding pharmacy is.

JRM Would these rulings affect all routes of administration?

Dr. Anderson Yes, they would affect anything compounded for any delivery route: topical, nasal spray, oral, suppository, and, of course, injectables. Most people who know something about the current FDA hearings think they apply only to sterile materials such as injectables, when in fact if the rules come into effect – if, for example, you want to make, or you want your pharmacy to make, a capsule that contains MSM and acetyl glucosamine or MSM and nicotinamide adenine dinucleotide mixed together – neither you nor the pharmacy would be able to do that legally. It would actually be illegal. The FDA changed the definition of "supplement" to mean oral delivery only, so supplements are exempt, but only if they are for oral use. So, something that is in a topical or suppository form is technically no longer a supplement. This is part of the reason why natural product companies that made suppositories quit making them a while ago. What's going on at the FDA is already having an impact even before any rules take effect. It's a very frightening situation.

Another confusing aspect of all of this is that substances used in integrative medicine that are currently approved as drugs are exempt from this process. For example, cyanocobalamin or hydroxycobalamin, which are the forms of vitamin B_{12} often used for injections, are approved drugs. They got approved a long time ago, so they are exempt from this process, and they cannot be "unapproved." Methyl B_{12}, however, was never approved for injections; it's just always been compounded. So, if the FDA votes "no" on methyl B_{12}, it will be a weird situation in which we can use hydroxyl B_{12} in an injection but not methyl B_{12}. A similar example is a form of injectable vitamin B_5, which has preservatives in it and is an approved drug. If you were to have the same thing compounded, however, it would be illegal because B_5, pantothenic acid, is on the FDA "no" list.

JRM If these rules get enacted, will it also make it much harder to do research on complementary and integrative medicine?

Dr. Anderson For sure. The question has come up, how will we do any innovation and research if these substances are no longer available? Researchers would have to apply for an IND (Investigational New Device/Drug), which the FDA would need to approve. It would be hard to get enough funding to go through the IND application process, let alone conduct a research study. During the hearings, I read into the federal record the clinical trial number of an ongoing study in which infusible quercetin is being used in cancer treatment. I said if the FDA enacts its ruling, this part of the trial would have to cease. The FDA said it should have had an IND in the first place, but this is not true. Under the current rules, investigators don't need an IND for a natural product that can be safely compounded. So, it becomes another catch-22 to say we could get INDs, when really only pharmaceutical companies have the funds to do that. It would shut down a lot of innovation as well as ongoing research on natural substances that already have a strong evidence base. Curcumin has about 55,000 citations on PubMed, and quercetin about 19,000. Yes, if these rules get enacted, it would be damaging to patient care on a number of levels.

JRM What is the current stance of the FDA toward injectable hormones?

Dr. Anderson The FDA is not currently including hormones in this hearing process, but we are told by our lawyers in Washington, DC, that they have a separate process in the works, the purpose of which is to go after bioidentical hormones, which they consider no different from synthetic hormones.

JRM Tell us more about the people, such as yourself, who are testifying to the FDA in support of keeping compounded natural substances available.

Dr. Anderson The people who testify in defense of these substances are part of a coalition that is made up of compounding pharmacy associations and a number of integrative medicine groups comprising largely MDs and DOs, as well as the AANP (American Association of Naturopathic Physicians). This consortium works together and consists of smart people. The people who do the testimony in support of a natural substance have the best knowledge of it, but unlike in a court of law, the FDA committee doesn't have to be swayed by what is presented to them. Here's what actually happens. The FDA hires independent contractors who don't work directly for the agency to run the panels. They are usually physicians or heads of pharmacology departments and, so, also smart people. A number of them have potentially very high conflicts of interest because they receive funding from pharmaceutical companies, but the FDA waives these conflicts. This issue was brought up at the last hearing and is recorded in the public records.

JRM What actually happens at a hearing?

Dr. Anderson The first thing that happens at these hearings is a slide comes up from the FDA which states that the FDA's panel of experts believes this substance – say, quercetin – should not be approved for Section 503A bulk compounding. The FDA essentially tells the committee how it would like them to vote. Next, one of the experts contracted by the FDA gets up. They usually have 45 to 60 minutes to present their data supporting why the FDA said no. Then, the opposing expert, such as myself, gets up and has 10 to 15 minutes to respond. So, just from a basic math point of view, it's not a terribly fair process. In addition, and more importantly, what the FDA expert presents about a natural substance often uses out-of-date evidence or sometimes, frankly, is a misrepresentation of data. Again, everything

is recorded, and this is all available to see in the public records.

JRM So, even when you present robust, up-to-date evidence, the FDA is under no obligation to take that into consideration?

Dr. Anderson Right. It's not like a court of law. There was another natural substance where the FDA material stated that there is no modern evidence supporting its use, but we had 15 citations in peer-reviewed journals just in the last 5 years. I showed these to them, and the response was, "That might be true, but we don't have to consider any of these references." It's possible to rebut what the FDA expert says with up-to-date evidence, but if the FDA doesn't want to take it into account, they don't have to.

JRM Given how hopeless the situation sounds, is there any point to you and our other colleagues still testifying at the FDA hearings?

Dr. Anderson We have to go through the process. We have to show that we made an attempt to fight back legally, and then if we are able to bring an injunction to this process and get it before a federal judge, we can say we did all that we could and the process is not a fair one. So, the reason we are doing this is because if we don't put up a good defense and aren't seen to be fighting it, no federal judge will review what happened.

JRM If these rules are enacted, when would they take effect?

Dr. Anderson The FDA is not telling us when this is going to happen. Our lawyers say they probably won't enact anything until they are done with all the hearings. The FDA reviews about six or seven substances per hearing, and as of now, probably three or four hearings remain, so not that many. As soon as the rule gets enacted, it will be illegal, with immediate effect, to make or to purchase for production any of these substances. Not telling us when it will be enacted is a big power play. I've heard people say that the FDA works very slowly and that this could take between 1 and 5 years, and other people say that it could likely happen in early 2019. If the FDA made a substance illegal every time it held a hearing, more people would have noticed the impact by now. But because the FDA is not taking things away until all the hearings are done, it makes the outcome of this process feel somehow more theoretical. It's hard not to think that this is a deliberate strategy to prevent people from getting up in arms. But people do need to do something now.

In terms of next steps, I think more avenues for clinician and patient involvement will open once legal proceedings start, so please keep your ears and eyes open, and let's keep the word out there.

More and more people are aware of these FDA hearings and the effect that they could have, but it's almost like it's too hard to believe it's real, because the implications for integrative and complementary medicine would be horrible. I've attended the hearings; I've read all the documents; I've testified; and it still seems too hard to believe!

JRM Dr. Anderson, thank you so much for educating us about this crucial and complicated issue and for being an ambassador on behalf of integrative and complementary medicine.

Paul Anderson, ND, is a graduate of the National University of Natural Medicine and a full professor at Bastyr University. He is cofounder of Advanced Applications in Medical Practice and is a well-known continuing education presenter specializing in complex clinical medicine, intravenous and injection medicine, oncology, and genomics. Dr. Anderson has participated in National Institutes of Health – funded research in integrative oncology and is coauthor of *Outside the Box Cancer Therapies: Alternative Therapies That Treat and Prevent Cancer*. He has also authored or coauthored numerous peer-reviewed and educational publications in science and health.