December 2011 Issue | Susan Brienza, PhD, Esq Regulatory Attorney

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Welcome to *Functional Medicine Update* for December 2011. Let me start this issue with a little bit of a provocation. We all have learned certain aphorisms that indicate or symbolize things that are beyond words. Let's use the little aphorism "An apple a day keeps the doctor away." What does that really mean? Or another little sound byte that appeared in marketing for Wonder Bread, a white enriched bread, and that is "Helps Build Strong Bodies." What do those sound bytes mean and how do they relate to the future of functional medicine, nutritional medicine, and nutritional therapeutics in the age of a rising tide of chronic disease? That question really attaches to what we see happening in our environment today, and how patients will be managed in the office, and ultimately how that translates into the evolving future healthcare system.

So that's the theme of this month's *Functional Medicine Update*, and we're very, very fortunate to have as our senior consultant/representative/opinion leader today a person whose background, as you will see, is very different than anyone that we have ever had on *Functional Medicine Update* over its 30-year past history. I believe it could not have come at a more timely moment to have this expertise shared with us on *Functional Medicine Update*. I don't want to spill the beans yet and tell you exactly who you're going to be listening to, but I do want to say if you keep your ears "peeled" (using my apple analogy), that you're going to be very, I think, interested in the message and the story that will evolve over this month's *Functional Medicine Update*.

Scientific Interest in Biological Response Modifiers has been on the Rise

Let me say a couple of things in preparation for where we are going to go. We've talked a lot about the bioactive ingredients in foods and natural products as being a focus of discussion and study at higher levels of scientific inquiry than in the previous, say, 50 or 60 years. If you follow the research citations that are being published in the world's literature, you will see an exponential increase in the number of studies, both basic science and clinical science studies, that are being published around the role of various of food-derived or natural-product-derived materials in modulating physiology in humans. Therefore, we would call these substances biological response modifiers. An example of this would be essential omega-3 fatty acids, the long-chain polyunsaturated fatty acids such as eicosapentaenoic acid or docasahexaenoic acid (EPA and DHA).

EPA and DHA: What History Tells Us About Study and Acceptance

We could go all the way back to the early 1980s, during which the first studies were being published

around the potential role of essential fatty acids in human physiology. I recall a paper in the *New England Journal of Medicine* by Elias Corey and his colleagues at Harvard.[1] They had done some of the first work published in a high-level, peer-reviewed medical journal on the role of EPA fish oil supplementation influencing leukotrienes and influencing monocyte activity (meaning immune system activity) in humans, and inflammatory response. That was some five to six years after people had started to recognize that the observations made by Dyerberg and Bang in Greenland with Hugh Sinclair, an Oxford Medical School professor and nutrition expert, on Greenland Eskimos who were consuming high levels of fat in their diet as oils rich in EPA from marine animals, particularly seals, and that these very high fat diets were associated, in these individuals, with the low incidence of cardiovascular disease and a very significant reduction in thrombotic events, meaning thinning of the blood.[2] When they studied the relationship between these high fat diets and the health outcomes in these individuals, they found that it was a consequence of the consumption of these high levels of omega-3 long-chain polyunsaturated fatty acids. So that goes all the way back into the 60s and 70s, these observational studies with the Greenland Eskimos.

You probably recognize that at first this was considered kind of artifactual because the dominant thought of the body politic at that time was that fat was bad, and so how could there be good fats when we recognized that too much fat was the cause of heart disease? We got into this paradoxical situation. I recall, actually, in the early 1980s, being a consultant for the RP Shearer Company. It was the first company to actually commercially sell fish oils in the United States under the name MaxEPA, and I was involved with the media tour We had done some research on fish oils at the university (I was overseeing a research group at the time as a professor). It was considered quite heretical to thought that oils or fats would be good. I recall getting very critical questions asked of me, and a lot of I-can't-believe-it type of response that these could be beneficial.

From the early 1980s fast-forwarding to today, literally thousands of papers have been published on the nature of the bioactive ingredients in these marine oils that have these dramatically interesting effects as biological response modifiers. We would call them pleiotropic effects, meaning effects across multiple actions or functions of the body. It has taken that 25 or 30 years to evolve a general state of understanding as to the positive benefit of omega-3 fatty acids in the diet.

If we really start looking at a lineage of ideas and how we've evolved our understanding over 30 to 40 years, it's to start to recognize that there are molecules present in foods that are produced by the biosynthetic processes of plants and animals that then induce alteration in function of humans consuming them, and they can have both prophylactic and therapeutic effects, depending upon dose, and form, and delivery system. Those bioactives found in food, which we would call natural products, then have a range of potential benefit in a culture that is burdened with chronic disease that might be incorporated within therapeutic goods that we would call nutritional supplements, functional foods, medical foods, or other types of goods that could then help to reduce the burden of disease and impart positive benefit on reducing metabolic disturbances that we associate with things like diabetes, heart disease, arthritis, and cancer. That is been the summary of how this field has evolved: this increasing weight of scientific evidence that supports the value of these substances.

Through that, we have obviously seen some very interesting changes in the regulatory framework and the oversight of these discoveries as they get translated into commercial products and ultimately available to consumers. We call those dietary supplements in the United States. They have been regulated by the Food and Drug Administration, as you know, and also advertising claims by the Federal Trade Commission of the United States.

1994: The Dietary Supplement Health and Education Act Passes Creating a New Regulatory Framework for Nutritional Supplements

That ultimately resulted, as you know, in this most remarkable transition in American law, which occurred in 1994 (October), which was the passage of the Dietary Supplement Health and Education Act (DSHEA) that was passed by both houses of Congress and set up this new regulatory framework for nutritional supplements in the United States. Substances that had been in free trade or sold as nutrition supplements were called “Old Dietary Ingredients” (ODIs) that were grandfathered in as safe and did not require, at the time, extensive testing of toxicology or safety because they were assumed to be safe. That gave birth to the emergence of the new nutritional supplement industry guideline and regulatory framework surrounding not disease claims, but rather structure/function claims, where you could promote a specific product that was useful for the promotion and support of particular types of structure and implied function in the organism. This would be things like: “Product X is known to support proper immune function, or proper bone function, or proper brain function, or nervous system function.”

Many Discoveries Have Taken Place Since 1994 and the FDA is Reviewing DSHEA

Now with that as a context, what has occurred over these many years since 1994 is a change in the understanding of the role that these substances have within biological systems. We have also seen a change in the number of substances that are now known to be biological response modifiers. This discovery work has proceeded at a very, very rapid rate—as I said, exponentially—so the number of citations around new ingredients that are found as biosynthesized substances within plants and animals has increased dramatically. Also, the clinical proof of safety and effectiveness for many of these ingredients has increased in human studies as well. We’ve seen a changing of the architecture of the environment as it relates to these products that are derived out of foods, and spices, and other natural products, including things like traditional Chinese medicinals, or Indian Ayurvedic therapeutics, or Brazilian rainforest medicines, or traditional Native American medicines, like Echinacea, that have bioactive ingredients within the constituents of these complex mixtures, and how that then ultimately fits within this regulatory framework as described through the 1994 DSHEA.

We have seen many new dietary ingredients emerge on the marketplace that are now in commerce as part of the therapeutic goods available to the consumer. The FDA has just recently—in 2011—said, “You know,

we need to go back and take a look—a hard relook—at how we're actually regulating the provisions of the DSHEA, particularly this New Dietary Ingredient convention, and ask 'Are we making sure that we're doing the proper oversight at the FDA level to provide proper protection for the consumer as it relates to the safety of these products?'" That changing regulatory environment is part of what ultimately shapes the products that are available, the things that can be said about them, who controls their manufacture, marketing, and distribution, and how that ultimately could influence patient management with a complex array of bioactive ingredients that are derived out of natural products.

Lovaza is a Fish Oil Product that has become a Blockbuster Drug

With that said, let me go back to the fish oil story. Once again, I think it is instructive in helping us to understand how that translates or maps against the overall changing of the architecture of this regulatory framework and the available products. So what's happened, over the last couple of years, is a certain product called Omacor, which was a fish oil supplement, went through clinical trial work and regulatory oversight as an investigational new drug for the management of triglycerides in patients that have elevated triglycerides, into an FDA-approved formulation of fish oils, which was then purchased by one of the world's largest pharmaceutical companies, GlaxoSmithKline, and rebranded as Lovaza, which is a therapeutic fish oil specifically designed (or let's call it "labeled") to treat a medical condition called high blood triglycerides, or hypertriglyceridemia. This product then became a number-one-selling fish oil product. Generating over a billion dollars of revenue, it would be considered, in the context of the pharmaceutical world, to be a blockbuster drug. It is said that a blockbuster category in the pharmaceutical world is a product that sells a billion dollars or more annually. This fish oil product became the first, really, nutritional supplement to become a blockbuster drug in the pharmaceutical world as Lovaza. As such, this product also, on formulary, was able to command insurance reimbursement as a tier 2 or tier 3 drug, and therefore it had a fairly high co-pay, but it was still considered "insurance reimbursed" for a medical condition called hypertriglyceridemia.

I think that this is a very, very important historical perspective that we need to be mindful of as it relates to the changing environment today within health care and how it affects functional medicine, which uses lifestyle medicine as one of its key therapeutic intervention tools. As you probably recognize, the translation of the fish oil story, or the omega-3 fatty acid story, from the 70s into Lovaza is a very interesting path of evolving science, evolving understanding, evolving consumer recognition, and then evolving commercialization ultimately into a proprietary product that has regulatory oversight as a pharmaceutical-like product.

Will We See More Lovaza-like Transformations in the Future?

With that in mind, one might ask the question: Does that then set the tone for what we are going to see happen in terms of nutritional therapeutics, or these bioactive ingredients from food and natural products that will occur in the years to come? Will we see more of the Lovaza-like transformations in which

something that emerges out of kind of a consumer product application in the nutritional supplement field ultimately becomes codified as a drug for specific clinical indication, and regulated by a different framework of the Food, Drug, and Cosmetic Act, no longer as a nutritional supplement, but more as a pharmaceutical intervention tool? And if so, what are the other ingredients or materials that might make this transformation, and how does it color the future of the availability of products and claims that can be made for these products within the field of nutritional intervention/nutritional prophylaxis and therapeutics? I find this a very important discussion if we start asking the questions such as how does medicine incorporate nutrition, and how does it get reimbursed, and how does it get incorporated into formularies, and where are the points of distribution for these products? This becomes part of a medical systems question as we are moving to recognize that our present is not really effective in beating back the rising tide of chronic illness. We need a different solution to the problem and we've been speaking to this extensively for years in *Functional Medicine Update*, with the interviews we've had with clinicians and researchers talking about different ways of approaching this. Halsted Holman, from Stanford,particularly did an eloquent job of sharing with us his views about the need for a new clinical education, and more patient involvement, and patient-centered medicine, and how that can be incorporated within a distributive medical system that is less involved with hospital care and more involved with self care.

I think all of these are points on a curve that are painting a picture of where medicine will go to try to more effectively and cost-efficiently deal with the rising tide of chronic disease. We recognize that 70{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} or more of these conditions that we see as burdening the global community with the rising tide of disease are lifestyle-related illnesses. That's not revelation; that's become an absolutely understood fact: that these lifestyle-related illnesses constite the major burdens on our healthcare delivery systems globally. Therefore, lifestyle solutions are needed for lifestyle-related medical problems, and we recognize that as part of lifestyle, nutrition plays an important role. It is not the be all and end all, but it is certainly a major component of what we consider lifestyle modifiers of physiological function that translates into disturbed metabolism and ultimately into disease. Functional impairments in physiology that occur from altered lifestyle translate later into discrete disease diagnoses.

What's the length of time for the trajectory to go from a functional disturbance ultimately to a disease? We could argue about that based upon the genetic uniqueness of the person and the degree of the strength of the signal of the disturbed metabolism, but I think that we would all agree that ultimately these conditions move forward in the trajectory towards increasing severity and increasing pathology, in which eventually a very clear diagnosis of a disease will result. The functional decrements of changes or disturbances are the early stage signs of the shifting of the sands that ultimately will give rise to the need for expensive hospitalization and medical intervention. The variables for the modification of that trajectory are therefore lifestyle-related. They are not drug-related, they are lifestyle-related. The question is: What role do bioactive ingredients within our foods play in determining the trajectory towards a chronic disease that becomes an acute disease, and how do you modify those signals by modifying those bioactive ingredients in the food or in the therapeutic intervention in such a way as to change the course of altered function and renormalize homeostasis of health.

Now we come to the regulatory framework in which these concepts are embedded. How does it get codified into standard of practice? How does it get codified into the regulation of prophylactic or therapeutic goods? How does it get trained and taught and ultimately implemented? What is the degree to which patients understand this and can actually make use of these concepts and have availability of the appropriate personalized agents that are necessary for restoration of proper function in states of disturbed metabolism that are individual to that patient's own unique state of health and genotype?

Those are very philosophically high-brow questions, but they really translate daily into how a healthcare practitioner speaks to their patients in that intimate moment within the exam room. The fish oil example is really a very important case history of a more general sense or discussion as to where we are going to go and what's going to be happening over the years to come. With that in mind, let's take a little window or a snapshot of the therapeutic category called medical foods.

The Medical Food Concept

We're going to talk about medical foods with our key expert today. I think the medical food concept was born out of the recognition of genetic metabolism diseases of infancy and the need for specific formulations for children born with unique requirements. Of course, the one that comes to mind immediately is fetal ketonuria, in which if you fed the infant the diet that is rich in the amino acid phenylalanine in the protein, that would then induce, as a consequence of the genetic imperfection and the metabolism of phenylalanine, phenylalanine toxicity, which then would translate into retardation and early death. But if you feed these infants a defined food that has a protein constitution that is limited in phenylalanine, now you have avoided this metabolic block in their genetic programming, and as a consequence they do not have the build up of the toxic metabolites and they can lead a fairly normal developmental pattern in life. So that defines a medical food for this genetic metabolism disorder of infancy . It's a protein-like formula that is devoid of phenylalanine as one of the essential amino acids. In fact, it would have tyrosine in its place as the downstream metabolite of phenylalanine by an enzyme called phenylalanine hydroxylase, which by the way, is the enzyme that is genetically altered in children that have PKU syndrome; they can't convert phenylalanine to tyrosine as effectively as a consequence of the altered genetic programming for the synthesis of the enzyme, phenylalanine hydroxylase.

This condition gave birth to the concept of foods for special dietary purposes (or therapeutic foods), and ultimately, then, a definition for medical food, which is a food formulated to be consumed or administered enterally (that means by mouth) under the supervision of a physician and which is intended for the specific dietary management of a disease or condition. I want to emphasize: It is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements based on recognized scientific principles are established by evaluating the patient medically.

So that's the definition of a medical food as contrasted to a dietary supplement, a nutritional therapeutic, or a functional food, or a food with National Food Labeling and Education Act health claims associated with it. This is to be prescribed by a licensed healthcare practitioner, and administered under the oversight and care for specific nutritional needs as exemplified by this disease condition or health state.

I think now the question is: Once you have this category, how does it get differentiated in terms of its proof of concept from that of a traditional food or a dietary supplement? We're going to be talking about this at greater length, but one of the things that we recognize is that it requires some degree of clinical testing to demonstrate its proof of concept, that it is, in fact, a therapeutic food for that specific medical condition that will produce measurable outcome for that condition that is positive and it meets the specific nutritional needs of that medical condition or diagnosis. This is an interesting category that has remained, I think, over the last 20 years, a category not really well understood either by the medical field nor the healthcare consumer. Food is considered to be kind of like energy. It is considered to be something you eat for hedonic pleasure. It has something to do with satiety. It's not something that you would think is a medical component of your daily environment. But what has happened—again using fish oils as the example—is over the last several decades we started to recognize that there are these bioactive ingredients that are found in foods that have therapeutic benefit in specific demonstrated need for the remediation or the support of people in specific disease states. These bioactive ingredients, like the use of omega-3 EPA for the treatment of hypertriglyceridemia can, in fact, be used therapeutically, and therefore they have more of a "medical" application.

More Rigorous Standards for Medical Foods

In order for medical foods to have a medical application and be proven safe and effective, however, they have to be subjected to a higher standard of identity for clinical proof of concept, so they have to go through a more rigorous safety evaluation. These are things that are done through what we call Generally-Regarded-As-Safe-types of evaluations (or GRAS evaluations). They have to be put through certain kinds of clinical studies on that formulation that demonstrate clinical outcome in people with that disease state that are positive, that are better than they would have gotten from a normal ad lib diet, so it has a higher evidentiary standard, somewhere in between food and drug, for their support.

I think this is a very, very important chapter in our evolving understanding of the regulatory framework, of the technology that relates to lifestyle medicine principles such as diet and nutrition, and how these ultimately influence an outcome—the trajectory, in this case—of health and/or disease. So where are we going to go in this discussion? I think where we are going to go is to try to get you to understand why "an apple a day keeps the doctor away" has some interesting historical evidence as it relates to the complex ingredients within an apple: things like pectin, things like polyphenols, things like various vitamins that participate in functional support of an individual.

If you say, “Well, what’s the difference between an apple a day and prevention versus an apple or twenty for therapeutics?” That’s the difference between a good diet and a medical food. I’m using this as kind of an analogy, so one might consider concentrating specific principles out of that apple into a formulation that would be considered to contain GRAS (generally regarded as safe) ingredients for the specific nutritional needs of individuals in a specific disease state, and then you have to put that to a clinical test, so it might become a bushel of apples a day (again, I’m using that in kind of as an exaggerated example) for therapeutic remediation of a specific disease state. Or you might consider this other example that I used, which is “builds strong bodies.” That claim was for Wonder Bread, which we would now laugh at, wouldn’t we, to think that white bread enriched with a few vitamins helps build strong bodies? Taking that from the ridiculous to the more serious, you might say: How do you build a strong, effective physiology—a functional physiology—in an individual that has a specific disease state as a consequence of something like insulin resistance that appears ultimately as metabolic syndrome, or type 2 diabetes, or a condition of autoimmune disease, or of gluten enteropathy, in which maybe a gluten-free diet is required therapeutically to manage their specific genetic personal need to support proper physiology?

All of these are defining, really, the framing of nutrition and medicine. It is that controversy, that confusion, that regulatory ambiguity, and that degree of rising discovery—exponential understanding of the bioactives in food—that is creating the landscape of today and how that will ultimately see itself in the recommendations of health practitioners to their patients for specific therapeutic agents, not just nutritional supplements, but agents that actually modify the trajectory in that individual patient’s situation toward proper physiological function and away from disturbed metabolism.

With the interview that is coming up next, we’re going to take a very, very good snapshot of the regulatory framework of these goods: where they are going, how they are viewed by the Food and Drug Administration and Federal Trade Commission, and how that ultimately may shape, in 2012 and beyond, the therapeutic pharmacopeia that is available for intervention in patient management. With that, let’s move to our key opinion leader of the month.

THE INTERVIEW

Expert of the Month

Susan Brienza, PhD, Esq

Ryley, Carlock, & Applewhite

JB: You all know how much I look forward—and hopefully you as well—to this portion of our monthly *Functional Medicine Update*, which we have called the “Clinician” or “Researcher” of the month focus. You’re going to be very privileged because this is the first time in 30 years that we’ve ever had a professional in this specific area of expertise on *Functional Medicine Update*. Our expert this

month is Ms. Susan Brienza, who is an attorney.

Let me say something about why *Functional Medicine Update* would have an attorney, and specifically Ms. Brienza, as our expert. You can probably recognize that we live within this complex social milieu where things are interconnected and very, sometimes, what I would call like a multi-headed-hydra—almost like a network that is sitting behind the scenes but becomes a web that regulates activities, behaviors, and beliefs. Certainly that is the case in the very complex area of health, health products, and medicine. The regulations that underpin much of the activity that relates to licensure, and standard of care, and therapeutic goods is regulated by the Food and Drug Administration, as we all know, and it is interfaced in the United States with regulatory agencies of comparable responsibilities elsewhere in the world. There is a global interface of these standards of behavior in policies and procedures.

This area of natural medicine, functional medicine, integrative medicine, and therapeutic goods that come from natural products has been one of those very complex and sometimes hard to pinpoint regulatory functions of the government. As we know, we have the Office of Food and Drugs, but this blurring of the lines between foods and drugs has been obviously apparent as the science has emerged to recognize that drugs and foods actually travel through the same pathways of physiology and influence the same biology. We don't have pathways for drugs in the body and pathways for natural products and orthomoleculars in the body; they all share the same type of biology, just with different mechanisms of action often.

The blurring of the lines between what would be considered food and what would be considered a drug has really occurred as a consequence of change in our biological understanding of physiology and biological response modifiers. It is because of that context that I thought it would be very helpful to have an expert in this field, which Ms. Brienza represents, to help guide us through where we are in 2011, moving into 2012. I can't think of anyone that is better prepared to share some of these concepts with us.

Let me just give you a quick thumbnail of the interesting personality you're going be hearing from. Susan has a background in literature, actually. She was a university professor in the area of 20th century American and British literature, a PhD-level activity at the University of Pennsylvania. I'm convinced, knowing her now (I didn't know her at the time she was a professor), that she was a highly valued instructor because of her eloquence, and her academic rigor, and just her personal style. I bet she was a loved professor.

And then she had an opportunity to do jury duty. Many of us have had that opportunity, but in her case I think it influenced her in a much different way, probably, than most of us who do jury duty. She ended up in an interesting trial. She really was taken to this and found it extraordinarily interesting. It hit both an

intellectual and professional chord for her, so much that she ultimately made the decision that she would give up her university professorship and go back to law school after the age of 40. She successfully completed law school at Stanford, and then went into the kind of law that we're going to be discussing today that is engaged in the oversight and regulation of therapeutic goods, particularly now focusing on natural products and the medical foods/functional foods, and nutritional supplement categories.

So it is a very interesting history, and a very interesting series of background experiences that Ms. Brienza brings to how she would contextualize some of the things that are going on in our field today. Having had the privilege of working with her in a recent workshop on medical foods that we produced at the World Health Forum at Harvard Medical School earlier this year, I was very, very struck by her insight, her expertise, and really broad range of understanding of this field.

So with that as a context, you're in store for hearing from an individual who I think has a unique perspective on this whole area, which influences, as you know, everything we do. It ultimately attaches itself to guidelines, regulations, and the law, and translates into activities at the patient bedside. Susan, it really is wonderful to have you as our guest authority here on *Functional Medicine Update*.

SB: Thank you, Dr. Bland, for that introduction.

JB: I think the place we might want to start is how did you take this interesting history that I just kind of superficially summarized and translate it into a focus on the whole area of dietary supplements, natural products, and ultimately the legal implications of those?

Litigation Work Led to a Focus on FDA Law

SB: In my legal practice I worked as a litigator (trial law) for five years, and some of the cases there involved a failure to warn the consumer. That was one link. Also, the jury duty that you mentioned. One of the trials that I was a juror for was a product liability case, and it had to do with the defendant not using the state-of-the-art science in a particular glass container, so that segued into my interest in science. And then five years into my legal career I got a position at Patton Boggs in FDA law, and at that time there were several lawsuits pending, as you probably remember (this was 1997)—lawsuits against dietary supplement marketers making diet pills with ephedra in them. There is a very checkered history of ephedra, both scientifically and in terms of the FDA, and as we all know, eventually in 2004 ephedra-containing supplements were banned. So my first legal project was actually a merger of litigation and FDA law with those ephedra cases.

JB: That's a great way to cut your teeth in this field. That was certainly a very intense period of time. And now you are at Ryley, Carlock, and Applewhite, so I presume that you've taken your Patton Boggs experience and now moved it over, maybe, into a really interesting time and place in the history of this whole regulatory framework, which is what the Dietary Supplement and Health Education Act (DSHEA) will look like in its interpretation in the 21st century. Maybe you could tell us a little bit about it.

The Potential Impact of the New Dietary Ingredient (NDI) Draft Guidance

SB: Yes, I continue my practice in FDA law and also advertising law. Of course, the FTC has joint jurisdiction with the FDA in regulation of both dietary supplements and medical foods. You are absolutely correct that this is an interesting juncture—a very challenging time—some would say a crisis point in the supplement industry, and of course I'm referring to the NDI draft guidance, for which comments from the industry are due tomorrow. This NDI guidance really could impact 70{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the supplement industry and that statistic came from the *Nutrition Business Journal*. So it's really quite an important development. In my mind, and in the minds of other attorneys, and trade associations, and commenters in the field, this new NDI guidance provides new definitions of what a new dietary ingredient is, what even grandfathered-in dietary ingredients are, and essentially seeks to rewrite not just Section 4 and Section 8 of the Dietary Health and Supplement Education Act (DSHEA), but even Section 3, which is the very definition of a dietary supplement.

JB: For our listeners who may not be quite as understanding of the history here, let me just help us define some terms. Within the DSHEA, the 1994-95 act that set up the regulatory framework for dietary supplements, there were categories called "Old Dietary Ingredients" (or "ODIs") and "New Dietary Ingredients" (or "NDIs"). Maybe you can just differentiate those two for our listeners so we understand how they—in the law—were set up.

Explanation of the Current FDA Guidelines

SB: Sure. Old dietary ingredients are also called "grandfathered in" ingredients, meaning that any dietary ingredients in dietary supplements that were on the market before October 15th of 1994, which was the date of passage or enactment of DSHEA (the statute), were called "grandfathered in" and they were presumed to be safe. This is in a very famous Senate report that led up to the passage of DSHEA. All supplements are presumed to be safe unless they are new, and there's a certain logic to that: "New" meaning that they were on the market only after October 15th of 1994. For a new dietary ingredient, the

FDA requires—and this is under Section 8 of DSHEA—a notification (and we want to keep in mind not preapproval, not pre-market approval as you would have for a drug). It was meant to be a simple notification, 75 days before market, where the manufacturer or the distributor (and this could be the manufacturer of the supplement or the supplier of the ingredient) would send to the FDA a packet of safety materials that would show that the new supplement containing the New Dietary Ingredient (NDI) would be reasonably expected to be safe. I want to point out that that safety standard, as you know, is a lower standard than Generally Recognized As Safe (GRAS). It is also a lower standard than the Food Additives Petition that requires a reasonable certainty of safety among experts. So it was an important victory of the industry in passing DSHEA: 1) supplements were presumed to be safe, and 2) dietary ingredients were exempted from the GRAS requirement and the food additive requirement and that new dietary ingredients were held simply to this lower standard of reasonable expectation of safety (again, pursuant to Section 8 of DSHEA). But all of that is about to change if this new NDI draft guidance should become the final guidance.

JB: Before we get into some of the subtleties of the difference among food additive categories, GRAS, drugs, and dietary supplements, could you tell us what the proposed guidelines, if they were enacted, would mean for anything that would be considered an NDI? What would change under those new proposed regulations?

Explanation of Proposed Changes

SB: Certainly. Several important changes. Number one is the NDI guidance is requiring much more documentation to prove that an old dietary ingredient is in fact grandfathered in—much more documentation of records of, for example, invoices and certificates of analysis pre-1994, which of course are records that most people do not have. The director of dietary supplement programs specifically has said in numerous seminars and webinars that the trade association lists of grandfathered ingredients will not be credited at all, and therefore much more documentation will be needed. That’s number one.

Next, the FDA, with this draft guidance, is saying that any new formulation, even of older ingredients, if it is some newer combination of even standard vitamins and minerals—let’s say a children’s multivitamin—that will be considered an NDI requiring a notification.

Another very basic change is if an older dietary ingredient will be processed using a slightly different manufacturing process, or extracted using a different solvent (that sort of thing), that will be considered an NDI, and then this notification requirement will kick in. And for the notification the FDA is now requiring a much higher level of science in terms of detailed toxicology tests, carcinogenic tests—just way beyond more traditional animal studies. That’s why I indicated that the tests and studies now required are more like for a food additive petition or a GRAS petition. Just as one example, instead

of something like an LD50 test, the FDA is requiring that your new dietary ingredient be safe at twenty thousand times the normal serving size. So it is a very, very high level of restriction, which some people are convinced have been the requirements, kind of behind the scenes, in the FDA's evaluation of NDI notifications during the intervening 17 years, we just haven't known about it. As you probably know, the percentage rate for the pass/fail rate is about 50-50 at best, meaning that most NDI notifications are not successful the first time around. Sometimes they are accepted on the second try.

JB: Yes, I think that's a very good overview for our listeners. I think that one of the takeaways that people are thinking about as they are listening to this (the way you are describing it) is in complex formulations, such as traditional Chinese medicinals, or Ayurvedic formulations, where there may be multiple ingredients from different plant sources that are all put together, the imposition of this kind of a new interpretation of an NDI and the regulation as it relates to proof of safety under the terms of this proposed rule-making sounds like it would make these types of products extraordinarily difficult to pass muster under this higher level of scrutiny, and would certainly be a tremendous financial burden to the industry to go through each one of these formulations with the kind of rigor that we're talking about in terms of new toxicological methodologies, further proving the proof of safety. It sounds like this would be very cumbersome, very expensive, and probably would end up—under the terms of these guidelines—in many products being unavailable.

Costs to Meet New Standards Could Be Exceptionally High for Supplement Manufacturers

SB: That is exactly correct and I like your example of the Chinese herbal formulas. One of my clients has a traditional Chinese herbal formula for a supplement with over 20 different ingredients, and all of these ingredients, of course, have been used in China for centuries. But under the new NDI guidance, if that particular collection of the 20-plus herbs was not on the market in precisely the same formulation pre-1994, it suddenly becomes an NDI requiring a notification. And you are right about the cost of all of these tests and studies that are now required under the guidance also. There has been one computation by an economic expert retained by Jonathan Emord, who of course is the famous (almost infamous, to the FDA) litigator and regulatory attorney. It was Jonathan Emord, just as a footnote, who has won six or seven famous federal cases against the agency, including the famous case in which the court required the FDA to permit qualified health claims, such as "Some studies show that walnuts may reduce the risk of heart disease." Jonathan Emord, in representing the Alliance for Natural Health, actually retained an economic expert, I believe from Emory University, and she reviewed the draft guidance very carefully and estimated that it would be up to over a million dollars for every single NDI notification, and under the new guidance some companies would have close to 100 NDIs (so-called NDIs).[3]

JB: Yes, I think we're starting to recognize that this is a major potential change in the implication to the industry that supports natural products for both prevention and therapy. I guess we're going to have to stay closely tuned to watch how this plays out. Certainly this won't be a knee-jerk decision. There will be—I would hope—adequate time for spar and parry on this and that rationality will prevail. But I think it is important for our listeners to recognize that this is a very important changing landscape that is not occurring only in the United States. This is interfacing global regulatory change in the review of safety-related questions or issues pertaining to dietary supplements. It occurs in Europe. It occurs in Australasia. It seems to be a very interesting change of the tide.

SB: Yes, you're correct, both in safety and efficacy. I believe the latest development in Europe is that the EU organization is getting tougher on permitting various health claims.

JB: Obviously we could spend—and you do spend—hundreds of hours on this topic, but let's shift over to a category that is also regulated by the FDA, that really relates very closely to probably many of our listeners who are practitioners that are treating patients with various illnesses and are using lifestyle medicine/nutritional medicine as maybe a component of their practice. This category is called medical foods, which is not directly under the DSHEA; it's a separate category. It has a different history, coming out of the F.D. & C. regulations, and it had, also, its own changing domain in the 2011 year. Maybe you can tell us a little about where medical foods came from and how does it differentiate itself from dietary supplements?

More Detailed Explanation of the Medical Foods Category

SB: That's a huge question, but I'll start by saying that in some ways "medical foods" (the name itself) is a type of misnomer and is very confusing to many people, even to MDs. One way to think about a medical food is that in terms of nutrition science and in terms of regulatory law it is almost precisely in the middle between a dietary supplement and a prescription drug, and I can talk more about that in a few minutes. The "medical" in medical food has to do with the medical purpose of the product, and the "food" has to do with the fact that these are all food-based ingredients. So most of the ingredients in a medical food would be the same ingredients that you would find in a dietary supplement—vitamins, minerals, amino acids, botanicals—but they are in a different formulation and very often in greater amounts. The most critical difference, though, between a medical food and a dietary supplement is that a medical food is used for the dietary management of a particular disease or abnormal condition. That's its intended use. So, in that sense, not only may you make a claim having to do with a disease (in this case, though, dietary management, not treatment, of that disease), but you actually must make that sort of claim ("For the dietary management of X abnormal condition") or the product would not be considered a medical food. Of course, as you and your listeners know very well, for a dietary supplement you may not make a disease claim or a drug claim of any sort, but simply a structure/function claim. So those are the key differences.

JB: So it would sound, from the way that you have described a medical food, that it has kind of a higher authority associated with it as it relates to intended use, in this case a therapeutic use for a specific medical condition. I guess the question our listeners would have is whether maybe all dietary supplements should be labeling themselves as medical foods and get around these NDI new proposed guidelines, but there are some things that I guess we need to know about as to why there is a differentiation in labeling between a medical food. Maybe you can help us to understand the difference between a dietary supplement and medical food as it relates to proof of safety and efficacy.

SB: Sure, and it is not a simple matter of merely changing the label, changing the statement of identity from dietary supplement over to medical food and then you are suddenly permitted to make dietary management of disease claims. First of all, the medical food is not exempted from the GRAS requirements as are dietary ingredients for a supplement, so all of the ingredients in your formulation for a medical food must have either GRAS status or must be an approved food additive. But you are also right, Dr. Bland, in your suggestion that clinical trials are in essence required for medial foods, whereas they are not for dietary supplements under current law.

JB: I think that's a very, very important point of differentiation. It's interesting—you and I had some discussions when we were back in Boston at the World Health Forum talking about the medical food category, in which we both were commenting about, in dietary supplements/nutritional supplements, because there is no direct claim that is allowed for therapeutic intervention, then the question of safety and efficacy becomes a very interesting question because you could prove safety, but if you can't make a therapeutic claim then you assume it has no efficacy because you can't say anything about it. When you look at risk/benefit, risk is a safety parameter and benefit is a therapeutic value kind of benefit, and if you assume that it has no ability to have a therapeutic benefit then the risk/benefit equation becomes entirely focused on risk with no benefit. And now you have to have something that is as safe as water to have value. These are very interesting regulatory sticky wickets, I think, as it relates to how you actually would use a natural product in a medical application, and this proof of safety and efficacy as a medical food appears to me to be much more in line with where most doctors might be applying a nutritional therapeutic versus a nutritional supplement. I'm kind of generalizing here, but maybe you want to comment from your perspective on that.

SB: Okay, in the case of both medical foods and dietary supplements, showing both safety and efficacy is the responsibility of the manufacturer or marketer. I'm switching now to efficacy. A dietary supplement claim is in the form of a structure/function claim, something like "Green tea extract helps support the immune system." That is an efficacy claim even though it is not a therapeutic claim, and under both the FDA and the FTC (for advertising), that claim must be supported by—and here's the standard from the FTC—"competent and reliable scientific evidence." But the key difference between the two types of products (medical foods and supplements) is that for supplements, traditionally (and this is

still permitted under current law) the manufacturer or marketer may use for scientific support what some people call “borrowed science,” simply the existing scientific literature, even existing scientific studies done by someone else or some other company, as to each of your individual ingredients. And there is no requirement—again under current law, but this could change in the coming years—to have a clinical trial on the precise formula in your current dietary supplement products.

Dr. Bland, you are exactly right, there is no DSHEA, there is no set regulatory schema, with detailed regulations for medical foods, so there are a lot of legal judgment calls that need to be made. But from the existing documents, which include a guidance document and a few others, and from some warning letters to medical foods companies who have had some violations, it is fairly clear that the formula itself must be the subject of clinical trials to show that your particular medical food really does have therapeutic value for the endpoints of the disease for which you are claiming dietary management.

How Does a Therapeutic Claim Differ from a Structure/Function Claim?

JB: I know we’re now into the deep morass of medicolegal technology, and languaging, and interpretation, but if we start looking at what is considered a therapeutic claim, as I recall it was a very broad definition of intent to treat, manage, or even prevent a disease, so you get into does prevention claims also lop over into what are considered therapeutic claims, or is it just in the treatment of a disease in and of itself?

SB: That is a great question. I think what you are referring to in your series of words there is one of the legal definitions of a drug. So here what we need to do is distinguish between a medical food and a drug. Even though in a 2007 short guidance document the FDA does say (and in the one regulation the FDA does provide) that a medical food has therapeutic value, it can be only in the form of dietary management of the particular disease. Now let me give a specific example here because I think it will be clearer. I’m thinking of osteoporosis or osteopenia, which certainly meets the threshold issue for a medical food, and that is: “Is this a disease that is characterized by a distinctive nutritional requirement?” The answer of course is yes. Someone with osteoporosis is missing the particular nutrients in their body that are absolutely essential for bone growth, not just maintaining bone, but growing the bone. So that medical food must have good evidence that it is therapeutic for the dietary management of the disease, not that it cures it, not that it prevents it. And in fact, there are at least three warning letters sent to medical foods marketers in which the FDA objects to improper claims for the product that either state or imply that the product will actually prevent a disease. So the only types of products that can make a disease prevention claim are drugs, or interestingly enough there is a certain type of prevention claim that may be made for foods and for dietary supplements, but it is only under the rubric of the preapproved health claim (the authorized health claim). I can give an example here, too. Of course a classic health claim would be: “Calcium may reduce the risk of osteoporosis.” That’s a claim that can be on your milk carton or on a calcium supplement. But ironically enough (or maybe logically enough), a medical food for the dietary management of osteoporosis may not claim “prevents” osteoporosis or even prevents

osteopenia.

You might remember there was a famous case about five years ago where about 26 marketers of cherry juice (cherry products, but primarily cherry juice) received warnings from the FDA saying: "You may not make a health claim about 'Cherry juice may reduce your risk of cancer' because that is not an authorized health claim that has been preapproved by the FDA." Same thing in the POM Wonderful case, where the POM Wonderful company was making claims about how pomegranate juice or pomegranate supplements may reduce the risk of prostate cancer or breast cancer. The FDA, and actually the FTC in this case, prosecuted that particular violation and said there is no authorized health claim. There may have been some pretty good science, but not significant scientific agreement, so there is no health claim on which you can base this prevention of cancer claim.

JB: Well, I can see that you have job security for the next several decades.

SB: The more complex the better for me!

JB: Let me, if I can, kind of distill down to maybe a couple of sound bytes. I always worry when I try to do this that I have inappropriately distilled, but let me try this on you. Given that our listeners are practitioners in the main and they are asking, "Okay, this is obviously very confusing and I'm probably not going to go back to law school so it's going to get figured out by people like Ms. Brienza, who have a lot more knowledge than I, but what does this mean for me in my practice?" It would seem, from the way that I'm listening to this interpretation, and the changing playing fields of the NDIs and so forth, that for a practitioner who is managing a specific disease state, that if their products are labeled correctly (that means assuming that the manufacturers of those products have fulfilled the intention of the law), that a medical food product, which requires clinical studies on that condition with that product looking at what would be considered acceptable endpoints, would be a product that would have a history of therapeutic application to that condition and also a history of safety given that it had to have GRAS ingredients, which is a higher standard of identity for proof of safety, and therefore a medical food product would be a category, if properly labeled, that would more align itself to a physician's needs for those specific conditions. Does that seem like a reasonable interpretation?

SB: Yes. What you said is generally true, that a medical food can certainly be part of a healthcare practitioner's resources (it doesn't have to be an MD)—although let me drop another footnote here, and that is another requirement for a medical food, which places it closer to the drug category, is that it is intended for patients under ongoing physician care and a medical food must be administered under a physician's supervision. And that all makes sense given that it is for the dietary management of a

particular disease characterized by a nutrient or metabolic imbalance.

Let me now not be a total legal wet blanket, as I sometimes call myself, and give your listeners some good news if they are licensed healthcare practitioners, and that is that the FDA is on record as stating categorically that the FDA does not regulate the practice of medicine. I'm sure many of your listeners have heard that. What that means essentially is that it is absolutely legal/acceptable/permitted for any healthcare practitioner to recommend, or in the case of a medical food actually prescribe, a product for "off-label" use. So that is absolutely permitted. That's the particular physician's or healthcare practitioner's freedom and discretion under the practice of medicine. Now, conversely a marketer of a product may not promote it for off-label use. Take an example of a drug that has been in the news in the past couple of years. If a drug has been approved for, let's say, uterine cancer, a marketer—a company—may not promote that particular product for breast cancer because it has not been approved for that. That would be an off-label use. But that prohibition does not apply to recommendations or prescriptions by a physician.

Functional Foods is a Category that is yet to be Defined

JB: Thank you. I think that's very, very helpful. One of the other questions that might come up in the minds of our listeners is the differentiation between a medical food and a functional food, because we hear those terms being used now and actually some products labeled at "functional foods." Could you give us a quick differentiation between those two categories?

SB: Those are very different. As hazy as the medical food definition might sound, functional foods has a much broader and even hazier description. First of all it is important to note the term "functional food"—and you, Dr. Bland, may even have coined that term, I'm not sure, but certainly "functional medicine"—but there is no such regulatory FDA category as "Functional Foods." It is a term that the FDA is looking into because the agency certainly recognizes that functional foods of various sorts have been on the marketplace for at least 10 years, more like 15 years, really. So they are looking into whether there should be a category that would be exactly midway in between a conventional food and a dietary supplement. That's where the agency would probably place it. Who knows what the requirements would be, but most probably they would be permitted to make some structure/function or health-type claims.

The problem, I think, with the term "functional food," which in many ways I very much like, and which, by the way, is a regulatory category in other countries such as, for example, Japan, but a functional food can mean anything from fresh blueberries, which obviously have wonderful functions and benefits for our nutritional system and for our brains, so that could be called a functional food (or tart cherries), to some sort of conventional food that has been infused with a botanical or vitamin enriched. I think you remember—I can say this since we worked together on the workshop in Boston at the World Health Forum

and we seem to be in the same age group—the old commercial for Wonder Bread: “Helps Build Strong Bodies 12 Ways.” Well, that in a way is a functional food, but the FDA would call is a conventional food that is simply vitamin and mineral enriched. So you see the problem. It defies categorization.

JB: Yes, I think that what you’re again helping me to understand and probably our listeners as well is that within this regulatory environment, which clearly has some boundary fuzziness, that it appears as if medical foods as they are presently defined does mandate a certain requirement for proof of efficacy and even safety through the GRAS ingredient provisions that might give a little bit more clearer, I guess you would call it, regulatory oversight for a doc who is managing a patient and wants to know how a product relates to safety and efficacy to the condition of interest. I think I can see now how medical foods have risen to kind of a higher standard of identity than these other areas that I think are a little descriptively ambiguous.

SB: That is absolutely accurate, what you just said, and I do think more and more traditional MDs, not only NDs, are becoming more familiar with the category of medical foods. I was very surprised a couple of weeks ago when I saw my own primary care physician and was asking her if I could try a medical food instead of a drug and she said, “Oh yes, I’m very familiar with that product. Oh yes, their sales reps have been to visit me and are very knowledgeable about it and I’ve written many prescriptions for that product.” So I was happy to see that it is becoming more widely known.

JB: Thank you, by the way for the time you are spending with us. This is very, very valuable and very information dense.

SB: My pleasure.

JB: I’d like to close with just kind of a broad brush question. In your professional activities, which span quite a wide range of different areas of application to what we have been talking about, at Ryley, Carlock, and Applewhite, I’m sure that either your clients or firms at times have asked for your professional opinion as a soothsayer, as a forecaster, as a clairvoyant: What might the landscape look like on the horizon? We all are caught with the difficulty of not knowing what the future might hold. Do you have a sense as to how this is likely to work out, the new NDI proposed rule-making, and whether this will go back to business as usual, or whether there is going to be some degree of change, and whether medical foods as a category will continue to survive as a unique category? What’s your professional assessment as to the landscape?

Probiotics Could Come to be Defined as a New Category if Changes are Implemented

SB: Some bad news about NDIs and supplements and some good news about medical foods. The bad news is another big problem with the NDI guidance which I didn't mention earlier, and that is, as you might remember, Section 3 of DSHEA defines what a dietary supplement is, and of course it can be a vitamin, mineral, and actually a botanical, or any dietary ingredient that supplements the diet. That, of course, is where the huge and beneficial category of probiotics currently sits, and I don't need to tell you and your listeners all of the huge benefits of probiotics. It's a very important category of supplements. Under the NDI draft guidance, however, which of course was just issued in July, the FDA expresses grave doubts about: 1) the safety of probiotics, and also 2) whether it is a dietary ingredient at all, and states that because probiotics consist of living microorganisms, there is a chance that they should be reclassified as "Probiotics," in other words as if they were the same as a vaccine. Of course probiotics require pre-market approval by the FDA. So that would be a huge change and that could essentially wipe out or decimate at least the probiotic supplement industry. So that is the horror story news.

The good news is that I believe that medical foods, as a category, will grow and will be especially important for our baby boomer generation. I think that you and other researchers are showing more and more that up to 70{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of all diseases—certainly all chronic diseases—are fundamentally nutrition-based problems, or metabolic-based problems in the body. This is precisely what can be addressed via dietary management with a medical food. I think it is a wonderful window of opportunity for, say, the next five years even for companies to do good R & D and develop mew medical foods, which will be accepted, I believe, by the medical community.

JB: I can't tell you how much we appreciate this time spent with us. This is really, really important news to use. It sounds like we're going through an epic period of what I think is an interesting conundrum, because we're faced with the changes of a regulatory environment that probably could have unprecedented impact upon product suppliers/marketers at the same time that the basic understanding of the biology of natural products and how they influence physiological function is increasing exponentially. So we're getting more and more understanding of the important role that bioactive ingredients within foods have on regulating health and disease at the same time that we're seeing a very, very significant trend to regulate these categories with greater degrees of specificity and more requirements to manage it as if these products are drug-like in terms of proof of safety and maybe even efficacy. So it seems like that's the inevitable pincer movement, right? We've got two forces that are moving that are going to change outcome as it relates to how we've seen the environment over the past, say, 17 years. That would be my takeaway from listening to you.

SB: Yes, I think that's correct. What we might see is a shrinking of the supplement market or supplements becoming more drug-like in terms of both safety and efficacy testing, and real growth in the medical foods market. Medical foods, by the way, were defined in 1988, so before DSHEA.

JB: I want to thank you and we're going to keep our ears to the tracks and follow your work at Ryley, Carlock, and Applewhite very closely. What a magnificent resource you represent in your experience and knowledge. Thank you so much.

SB: Well, thank you. You were asking me terrific questions, so it brought out the best I hope.

JB: Thank you so much.

Closing

It's my hope that through this extraordinary journey we took with Ms. Brienza that you recognize that we are at a threshold period in our evolving understanding of how to manage chronic illness and what role nutrients and nutrition will play, and how they'll be regulated, and branded, and ultimately reimbursed for their application. This is an epic period. I mean, there is just no two ways about it. Over the next year or two, we're going to see very remarkable change in the way that this whole category and this whole field is managed, reimbursed, described, regulated, integrated within the standards of care. I would suggest that the healthcare practitioner, in the use of medical foods and therapeutic goods that are properly labeled will have a catbird seat in implementing this new medicine and fighting back against the rising tide of chronic disease. Stay tuned. More to come on *Functional Medicine Update*.

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