ORIGINAL

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FDA PROPOSED REGULATION

CURRENT GOOD MANUFACTURING PRACTICES

DIETARY INGREDIENTS AND DIETARY SUPPLEMENTS

PUBLIC STAKEHOLDER MEETING

Pages 1 thru 190

College Park, Maryland
April 29, 2003

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Tuesday, April 29, 2003

9:05 a.m.

Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, Maryland

MILLER REPORTING COMPANY, INC.
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C O N T E N T S

P R O C E E D I N G S

Welcome and Opening Remarks

MS. WILKENING: Good morning. I am Virginia Wilkening, the Deputy Director in the Office of Nutritional Products, Labeling and Dietary Supplements. I am very pleased to welcome you this morning to this meeting on FDA's Proposed Rulemaking on Current Good Manufacturing Practices for the Manufacturing, Packing and Holding of Dietary Ingredients in Dietary Supplements.

It is important that consumers have confidence in the dietary supplements they buy. That is why we believe this proposed regulation is a major step in the Agency's effort to help Americans take more control of their own health. By attending this meeting, you are taking an important step in understanding how the proposed regulation impacts the dietary supplement industry.

We also see it as a sign of your commitment to ensuring that consumers get dietary supplements that are accurately labeled and that are not contaminated. That is what this proposed regulation is designed to do.

For the first time, minimum manufacturing practices will be established that will help ensure

that dietary ingredients and dietary supplements are produced in a way that ensures the identity, purity, quality, strength, and composition of those supplements.

Now, that sounds like a lot to do, but our goals today are simple. First, we are going to provide an overview of the proposed regulation. The Agency's staff that have been involved in the development of this proposed regulation and staff with expertise on the technical matters are here to discuss the proposal with you and to clarify the points as needed.

Our second goal is to tell you the process for submitting comments to FDA. We want to receive your comments about what should or should not be included in the final regulation and we want to know what supporting information that you feel is important to that endeavor.

We want to emphasize that it is important that any comments you make today be submitted in writing to FDA docket to assure their consideration in the final rule. We have set a 90-day comment period and that means we look forward to your comments and your suggestions by June 11th of this year.

For your information, we have also set up additional meetings that I would like to just mention briefly. Those will be held on May 4th in Secaucus, New Jersey, concurrent with the Supply Side East meetings, on May 6th in Oakland, California, a meeting similar to this, and on May 9th, a satellite downlink will be held that you can hook into. Additional information on those meetings is available on our CFSAN web site under What's New.

The CFSAN staff gathered here today and I look forward to working with all of you on this effort.

I am now going to turn the meeting over to Peter Vardon, so that the experts can begin the discussion. First, I would like to briefly introduce Peter. He is an economist with our Office of Scientific Analysis and Support. He has worked on the economic impact analysis of many different regulations, but for today's meeting, it is important that he did the analysis for this rule.

Peter has been at FDA for 14 years and held various technical and managerial positions. He received his Bachelor's in civil engineering

from the University of Colorado, an MBA from the University of Denver, and is nearing completion of a Ph.D. in economics from George Mason University.

Peter.

MR. VARDON: Thank you very much, Virginia, and let me welcome you all. Thank you for coming on such a beautiful day.

Today, I am going to serve two roles. As Virginia mentioned I was an economist on this rule, so later in the program I am going to describe the economic analysis, but this morning I am also going to bring just a few housekeeping rules and tell you how we are going to proceed throughout the day.

You should have received a variety of handouts on your way in. I think there were about 10, and if you didn't receive them, they will still be there on your way out, so please take them with you. The handouts included the list of upcoming events, which Virginia just described, a fact sheet and Backgrounder, and a small business guide, which might help you also if you are a small business owner. We included a list of restaurants which were in the area.

We are going to have about an hour and a half break, so we hope that will give you enough

time to go to a restaurant, and there are a variety of restaurants on Route 1 if you know the area, but if not, we do have a cafeteria adjoining our building, so if you don't want to leave, you can certainly go there for lunch.

We are also going to have a couple of breaks throughout the program, placed strategically at mid-morning and mid-afternoon, and those breaks will be about 15 minutes each, and restrooms are near the registration desk on your way in.

We also ask that you turn off your cell phones and pagers, so that we don't disturb the speakers this morning, and we ask also that there are no food or drinks in this building or in this auditorium. We recognize we do have drinks up here, but we hope you will forgive the double standard.

As you entered the building, you probably received a visitor's badge. On your way out at the end of the day, we ask that you leave the visitor's badge at the guard's desk. If you go out to lunch, you will have to return and go through the magnetometer again, and we hope you will understand that also.

Let me just say a word about how we are

going to handle questions and answers. We do expect many questions today and we may not have time to address all of them although we are certainly going to do our best.

Just to ensure a steady, an even response to all the questions, we are going to ask that you write down your questions on a 3 by 5 card, and as you think of a question while the speaker is speaking, we ask that you just hold up your hand and give your card to a couple of the ushers, Janet McDonald and Monica Revel. They will be on each side of the aisle, each side of the auditorium.

Just pass your card on to them and then we will bring it down here, and then we will ask it, and we hope that this way we will be able to get to everybody's questions.

We are going to proceed with this program until about 12 o'clock, break for lunch, and we are going to return at 1:30. The afternoon session will be conducted a little differently. We are going to have a breakout session.

We recognize that this rule will have a significant impact on the industry and a significant impact on small business owners, so we wanted to create a special opportunity for small

business owners to meet with yourselves and discuss how this rule will impact you in special breakout sessions, small groups that will allow you to talk with yourselves about this rule, about how you think it will impact you, what questions you might have, and then we want to reconvene in this auditorium at the end of the breakout sessions and have some representative from each of the sessions summarize what you talked about in your little breakout groups, and we hope that will be a service for you actually.

We also have a transcriber in the booth. This is a public meeting, and so what is said here will be in the public record.

Let me introduce our next speaker. Our next speaker is Karen Strauss. Karen is a Consumer Safety Officer and Acting Team Leader on the Dietary Supplements Team, which is in the Division of Standards and Labeling Regulations.

Her work assignments include drafting of the Current Good Manufacturing Practices proposed rule and working with the Food Advisory Committee Working Groups on Dietary Supplements, and a variety of other regulatory issues with dietary supplements.

Karen has worked for 18 years with the Department of Health and Human Services Indian Health Service, and she was the Chief of Nutrition and Dietetics from 1991 to 1997. At the Indian Health Service, she served as the functional head of all nutrition and dietetic activities of the approximately 250 nutritionists and dieticians employed or contracted by the Indian Health Service or the Tribal governments.

She provided a professional guidance and conducted research to strengthen and improve the quality and scope of nutrition and dietetic services and community and clinical programs for American Indians and Alaska Natives.

In 1997, she transferred to FDA. Karen received her B.S. in secondary education from the University of Minnesota and her M.S. in food science and nutrition from the University of Wisconsin.

Karen is going to discuss the background of the rule and some highlights of the rule. She has been working on the rule from the beginning, so there is really nobody more qualified than her to give the next presentation.

Background and Proposal Highlights

MS. STRAUSS: Thank you, Peter.

I guess it's all that experience I had with projects and managing at Indian Health Service, that when I came to FDA, this was something that was assigned to me early on and has been the topic that I have worked on since coming to FDA in early 1998, first with the Food Advisory Committee Working Group on CGMPs for Dietary Supplements and then beginning the drafting process.

I want to acknowledge first before I start that there are many, many, many, many, many people that participated in the drafting process, some who were at FDA and have since moved on, gave us very good scientific advice in the very beginning, as well as many from industry who participated in stakeholder meetings and on the Food Advisory Committee Working Group, so there were many efforts that have gone into developing this proposal.

My part of the presentation today is to give you a background and an overview, and also give some highlights. I will talk about what CGMPs are designed to do, why the Agency developed the proposed rule. I will give some citations for legal authority that we relied on in preparing the

proposal, give some information on how the proposal was developed.

I will highlight some of the requirements, and one of the handouts that you received included the first few pages of a very lengthy document, and within those pages we have included a Highlight Section, and that section is there in the beginning just for that purpose, to give a highlight of the rule.

Then, at the very end, after the other panel presentations, I will come back and I will describe a bit about how comments would be helpful to us and then the next step in proposing the rule--excuse me--going from the proposal to the final rule.

So, what are CGMPs designed to do? Well, consistent with FDA's public health mission, the CGMPs are intended to help protect consumers from adulterated products. It is another way of saying from contaminated products.

Also, the CGMPs are intended to help protect consumers from products that do not contain what is claimed on the label. These two objectives are what guided us throughout our drafting process.

If the proposal becomes final as proposed,

it will provide consistent industrywide requirements to ensure that dietary supplements are produced consistently from batch to batch and ensure the identity, purity, quality, strength, and composition of the product.

It is important to note, however that CGMPs will not ensure the safety of a particular dietary ingredient, nor will they ensure that a dietary ingredient produces any claimed effect. However, I would mention under the Dietary Supplement Health and Education Act, which we call DSHEA, the manufacturer has a critical and very important role to ensure the safety and efficacy of the dietary ingredients they use in manufacturing a product.

I want to also mention that CGMPs will not affect consumers' access to dietary supplements and will not affect health and structure-function claims. It will not affect either any standards, such as kosher standards or organic standards.

More on why CGMPs. Congress saw a need by authorizing within DSHEA that the Department of Health and Human Services and FDA, by delegation, have the explicit authority to issue dietary supplement CGMP regulations.

FDA has found problems, manufacturing problems that have caused products to be recalled and there has also been independent lab testing that demonstrate need for CGMPs.

We received comments from industry and consumers at various stakeholder meetings that urged the Agency to give high priority to developing this proposal, as well as the industry, by submitting an outline of CGMP practices indicated their support for this proposal.

More on why CGMPs. I will mention some particular product recalls and independent laboratory testing that demonstrated the need and show some manufacturing problem. On FDA inspections, FDA found some poor sanitation that resulted in bacterial contamination.

There have been recalls needed because of ingredient misidentification. One very good example is Digitalis lanata was mistaken for plantain and some very serious heart reactions occurred.

There have been superpotents or dietary supplements that contained more than the label claimed. One example is selenium, a product contained from 2 to 20 times what was claimed on

the label, and high amounts could produce illness or injury.

Also, there have been subpotents, dietary supplements that contained less than was claimed on the label. In this example, a folic acid product contained 35 percent of what was on the label claim, and folic acid has a well documented role in preventing neural tube defects.

Also, there have been supplements that have been contaminated with prescription drugs, and these have resulted in recalls.

Consumers want assurance of product quality and there are several consumer studies that indicate that consumers want greater assurance of product quality. Consumer surveys show that only 37 percent of consumers thought that supplements were adequately tested before marketing. A majority said that there is not as much regulation as is needed to make sure that supplements are pure and dosages are consistent.

Surveys of over 50 said that they thought the Federal Government should review safety data and approve a product before it is sold, and only about a third of consumers were confident that products were accurately labeled. So, clearly,

consumers would benefit from having some manufacturing standards.

Also, because there has been publicity about manufacturing problems and about label claims not being present in dietary supplement products, there is some eroding strength of consumer confidence in the supplement products they purchase.

There are also some safety concerns about some products. Quality issues are also of some concern, and inaccurate or unsubstantiated label claims also are some challenges, and by establishing an industrywide CGMP standard, some of these issues, in fact, most of these issues can be improved upon.

I will now give you some of the legal authority that we relief on and are cited in the preamble. Section 402(g) of the Act, as I mentioned previously, gives authority to HHS and FDA, by delegation, to prescribe CGMP.

Within that authority, Congress gave two directions. One, it stated that the CGMP should be modeled after food, and other states that we may not impose a standard if there is no current and generally available methodology.

When we looked at the word "modeled," we went to Webster's Dictionary to see the meaning of modeled. A model is a preliminary pattern, so in developing this proposal, we looked to the food GMP as a preliminary pattern for our proposal.

There are some commonalities between the food GMP and in our proposal in that we cover the same kinds of activity, such as receiving, inspecting, production and process controls, packaging, segregating, processing, storing and distributing.

There are some similar sanitation requirements between conventional foods and dietary supplements, however, dietary supplements have their own unique set of characteristics, because there are different preparation methods, different dosage or ingestion forms, and the ingredients are different from conventional foods.

I am kind of looking back to my basic food background. If you think of distinguishing a green pea from a green bean, conventional foods, you can easily tell by looking at them the difference, but if you look at two white powders that might be made into dietary supplements, it is very difficult to detect the difference or the identity without some

kind of further testing.

Section 402 is the same section that deals with adulteration of a conventional food, if any product is filthy, putrid, decomposed, or otherwise unfit for food, it is adulterated.

Section 403 describes when a product would be misbranded or mislabeled. It gives authority for labeled nutrition information, supplement facts, that is. It also gives authority for identification of dietary ingredients sources, of botanical, so within that label, it needs to identify the dietary ingredients, as well as the quantity of each.

There are two other sections of the Food, Drug, and Cosmetic Act that we relied on for efficient enforcement. 701 gives authority for efficient enforcement, NFC section that we relied on for recordkeeping, and there are records required for other commodity-driven food or food manufacturing regulations in the CFR.

Section 704 gives authority to inspect warehouses, factories, and other establishments. Then, we also relied on Section 361 of the Public Health Service Act, and this gives authority for requirements to prevent introduction, transmission,

and threat of communicable diseases from state to state.

Thinking about animal-derived dietary ingredients and plant-derived dietary ingredients, they both come from natural sources, and could be contaminated by soil, by animals, or by handling during harvesting, processing, and transporting, so we rely on this particular act to help prevent communicable diseases from state to state.

Then, in looking at the process of what we would require, we really took a look at dietary supplements as a commodity.

We looked at how the products are manufactured, what equipment is used, what processes are used. We looked at the unique properties of dietary ingredients, whether vitamins, minerals, or botanicals.

We then used plain language techniques and in a detail that we thought would be necessary for a clear enforceable regulation, recognizing that a large percentage of the firms that manufacture dietary supplements may not be using any good manufacturing practices at all, we wanted to include enough detail that it would be understandable, yet still provide further process

and performance objectives.

Then, lastly, we considered the estimated cost and benefits in what we propose. We wanted to keep the cost and benefits kind of in balance, so that also influenced what we propose.

We looked at some outside sources and I think it would be interesting for you to know some of these that we looked at. The White House Commission on Dietary Supplements was established by DSHEA, and they issued a report in 1997, and they supported the industry and FDA working collaboratively to develop CGMPs, and they also supported CGMP recordkeeping as essential to substantiate label claims.

There is a Food Advisory Committee Working Group, and we look to this document, the report, for ingredient identity testing insight, as well as records and recordkeeping.

Then, in 1999, we visited eight manufacturing sites, and we did that, so that we could see what current practices were in place. We also had some small business meetings. We had three meetings in 1999, and the purpose of these meetings was to get input from small businesses on the kinds of requirements that were proposed in the

Advance Notice of Proposed Rulemaking, which is also the industry outline.

When we sat down to draft, we began with the foods CGMP, the umbrella food GMP, and we looked at that document primarily as to what was applicable to dietary supplements and what maybe was not. We took out what we thought wasn't applicable, but as we have done throughout the document, we asked for comments on whether, you know, we did that in the right way, whether we should put some things back in.

We also updated some of those requirements. For example, the definition of sanitation, in a comment to the ANPRM, we received a suggestion that we use the food code, not the food GMP, but the food code definition of sanitize, so we considered that.

We also knew that in the juice manufacturing requirement regulation, that definition is also in use, so we included that in our proposal. Maybe that is something that we will receive comments on that we need to go back to the old or what is currently in the food manufacturing practices.

We also looked to other commodity-driven

food GMPs. We looked at, for example, low-acid canned foods, juice, fish, fishery products, and infant formula, both the proposed and the established regulations.

Then, as far as organizing the proposal, we looked at other FDA GMPs. We looked at drugs and we looked at devices for those organizational principles.

Then, from the food GMP, then, we looked for the industry outline, got a lot of insight and information from the industry outline that was in the ANPRM. We also looked at USPs and in a phased outline.

This is kind of a schematic that shows kind of the organization and as we drafted, we started from the beginning where the component and the materials like packaging and labels come in. We looked at the warehouse where the materials are segregated.

Then, a manufacturer would need a formula or a recipe for producing that dietary ingredients or dietary supplement. We called this a master manufacturing record. They would produce bulk materials, bulk dietary ingredients or a bulk mixture of dietary ingredients and ingredients, and

we proposed flexible testing requirements.

Because of their certain challenges and in analyzing finished product, we allowed for some choice here, so you will see under Flexible Testing, there is a dotted line coming down first that goes before the bulk production and at bulk production, and another line that goes after bulk production, so a manufacturer has the flexibility to choose whether it should analyze the final product for identity, purity, quality, strength, and composition, or they can test the incoming and in-process to be sure that they start with the right materials and that along the way they are not contaminated.

Then, we move on to packaging and shipping. We also have requirements for consumer complaints, and those consumer complaints could tie back to anywhere along the manufacturing process.

We have records for certain stages throughout the manufacturing process.

Now, I will get into some of the highlights of the proposal. CGMP would apply to domestic firms. It would also apply to foreign firms that want to export dietary ingredients or dietary supplements into the U.S.

FDA currently has experience with foreign firms and if they have some questions or concerns about a product coming in, they currently have the authority to conduct some tests to see if there is a problem.

Also, firms that really want to get their product imported into the U.S. generally want to be in compliance with whatever regulations the U.S. has.

Also, there is a provision that the manufacturer would need to comply with other applicable regulations. An example here would be if a dietary ingredient includes fish oil, for example, the manufacturer of that fish oil would need to comply with Part 123, the Fish and Fishery Products Manufacturing Regulation.

GMPs apply to activities associated with manufacturing, packaging, holding, distributing, as well as things like labeling, testing, quality control, and distribution.

A manufacturer would need to comply with requirements applicable to the operation for foreign. So, if they are a packager or labeler, they would need to comply with those packaging and labeling requirements.

That labeler would also be responsible for the identity, purity, quality, strength, and composition of the dietary supplement that they are including in their package and the responsibility for the label, and we, at this point, left it to the manufacturer's discretion as to how they would ensure that the label matches the product.

Maybe in the final rule, we will need to add some detail there, but at this point, we are leaving it to the packager's and labeler's discretion.

The manufacturer would need to comply with the operations that were performed. If a contractor contracts with a packager or labeler to do that function for them, the manufacturer would be responsible to ensure that the packager and labeler followed the requirements for packaging and labeling that we have proposed.

The contracting firm would also be responsible, so there is really kind of a shared responsibility there.

We have proposed personnel requirements that really are consistent with the umbrella food CGMP, and they are basically to help prevent contamination. We would require that there be

qualified employees and qualified supervisors, that they must have the training and the experience to perform their assigned duties, but we have not prescribed what that training and experience involves. We have left that to the manufacturer's discretion.

The manufacturer would be required to take measures to exclude any person from operations who might be a source of microbial contamination, and they would be required to use hygienic practices to the extent necessary to protect against contamination.

The physical plant's internal environment, the proposed requirements really follow the food CGMP quite closely. Here, I want to point out some plain language techniques, which are to put a heading in bullets rather than a whole paragraph.

In some cases, it looks like there are more requirements, say, in our proposal than there are for food, the umbrella food GMP, when you look at the amount of space that's taken up, but if you look at how a paragraph is transformed into a heading and bullets, and carefully look at the bullets, they are in many cases just exactly the same as what is in the food CGMP.

Here again, the physical plant internal environment proposed requirements are designed to prevent contamination. Looking at the design and construction of that facility, that is, floors, ceilings, walls, can be easily cleaned and maintained.

There have to be separate areas or separate systems for specific operations to avoid mix-up and in screening to keep out pests.

We have included some requirements for maintenance and sanitation, and that water that contacts dietary ingredients or dietary supplements or that is used in manufacturing at the very minimum meets the EPA drinking water requirement.

We propose plumbing, bathroom, lighting ventilation and trash requirements to prevent contamination, and these also model the food GMP.

Equipment and utensil requirements. Again, these are to prevent contamination and the requirements, you would require that the design or selection of the equipment needs pre-established specifications. If you have a mixer, it needs to be of the right size and ability to actually get a homogenous mixture if that is the intent.

To maintain clean and sanitized equipment

and utensils, we have requirements for those, and we would require that instruments and controls be calibrated and that automatic, mechanical, and electronic equipment be inspected or checked to ensure proper performance, and in a general statement, that the manufacturer would be required to ensure that equipment functions as intended. We have not specified how they would do that, we have left that to the manufacturer's discretion.

Production and process controls. Sara will give more detailed discussion on this subpart, but, in general, we would require quality control unit, a master manufacturing and batch production record really to ensure batch-to-batch consistency, specifications for incoming, in-process, and final product, and the last bullet here, testing of final product or incoming and in-process materials again to reiterate the flexibility that we propose in testing.

Consumer product quality complaint. This is an area that is difficult to understand. It is kind of challenging because we have kind of eliminated one category of consumer complaints that would not be considered consumer complaints under this regulation.

Those that would be considered under the CGMPs include product quality complaints. Examples would be superpotent, subpotent or wrong ingredients, or a contaminant, a bacteria, pesticide, toxin, glass, lead or a drug contaminant.

The Quality Control Unit would be required to review product quality complaints to see if there is a failure of a specification or if there is some other CGMP that has failed.

If there is a reasonable relationship between the consumption of the dietary supplement and an illness or injury, the Quality Control Unit would be required to investigate that and to look at other batches that might be affected.

The firm would be required to keep consumer product quality complaints related to CGMPs.

The last bullet here, that a consumer complaint, as far as this regulation is concerned, is not related to a CGMP safety issue of a particular dietary ingredient independent of whether the product is produced under CGMP.

Holding and distributing requirements that we have proposed again model the food CGMP and

really here they are to ensure that the product is not adversely affected, so the requirement proposed includes appropriate conditions of temperature, humidity and light as far as holding and distribution, and under conditions that don't lead to mix-up, contamination or deterioration.

We have proposed records and recordkeeping requirements. The records that would be required to be kept would be those calibration records, master manufacturing records, and batch production records, as well as consumer complaints.

We have proposed that the records be kept for three years beyond the date of manufacture of the batch that would be associated with those records.

We have not proposed an expiration date, so we can't tie the record retention to that, and the reason we haven't proposed an expiration date is that logically, an expiration date should be tied to an active ingredient and because for botanical and herb, the active ingredient many times is not known, so we have not proposed expiration dating for the reason. We do ask for comment on whether there are certain dietary ingredients, such as vitamins, that should have

expiration date, and not other.

The other proposed requirement is that FDA would have access to records when requested.

At this point, I will introduce Sara. Sara is a consumer safety officer from the San Diego Regional Office. She joined FDA in 1998, and has focused her work on food inspection including dietary supplements manufacture.

During the summer of 1999, Sara participated with us in our site visits on the West Coast as we visited manufacturers, and then she also reviewed our very lengthy proposal and provided some very helpful comments on our proposal.

Before joining FDA, she taught ecology, botany, and general biology at the University of Puerto Rico. She has a Bachelor's degree in science and a Master's degree in botany from the University of Puerto Rico. While there, she was assistant curator of the university herbarium for three years. She has also a Master's in philosophy from the Department of Ecology and Evolution of the State University of New York at Stonybrook.

We are going to take some Q and A before Sara.

MR. VARDON: I do have some cards.

Our first question is concerning a proposed Subpart D regarding equipment and utensils. The questioner first states that much of the equipment and utensils used in dietary supplement manufacturing are identical to those used in food manufacturing including weighing systems, conveying systems, blenders, et cetera, and he asks, therefore, why doesn't Subpart D follow current food GMPs found in 21 CFR 110, isn't it inconsistent to say that it is acceptable for foods, but not for dietary supplements.

MS. STRAUSS: I think I have addressed that in that we really have followed the food GMPs very carefully. I think that perhaps there might be some differences in the calibration requirement for instruments and controls, but the instruments, equipment, and utensil sections really do follow very closely the food GMPs.

Having said that, in visiting the sites, we did see the kind of equipment that really is used in manufacturing tablets and capsules and gel caps, which is really different than the canning and freezing, and processing of food, so there are some differences, but I think if you will kind of

go carefully through the two, you will find that the food GMP and the dietary supplement GMP proposal, the equipment and utensils are really very similar.

If you think that there are some differences and you want to address that in a comment and explain to us why something should or should not included, we would be very happy to receive those comments.

MR. VARDON: Our next question asks about the fish oil compliance and is the fish oil compliance to cover only the fish oil manufacturer or finished goods containing fish oil.

MS. STRAUSS: Well, actually, as we proposed it, it would be both. As a fish oil is prepared, it would be a fish or a fishery product and would need to follow the CGMPs for fish or fishery products, so it would be both for the preparation of the fish oil as a fishery product manufacture. It would need to follow those requirements and then for preparing the dietary ingredients, the dietary supplements, it would need to follow any final rule for CGMPs for dietary ingredients and dietary supplements.

MR. VARDON: Our next question regards

personnel requirements, and the questioner asks why education, training, and experience instead of education, training and/or experience.

MS. STRAUSS: The preamble discusses this and I will see if I can capture it. Training and experience. We think that training is more classroom kind of background, and experience would be things that you had obtained on the job. We think that both are important, and it is not an either/or kind of thing. That is why we used the word "and."

MR. VARDON: This questioner asks about calibration. He states that the method seems to be left to the manufacturer's discretion, and he wonders what happens when you disagree with a manufacturer's determination that their method of assuring that equipment functions as it should is adequate for such a determination.

MS. STRAUSS: There are certain established general principles of instrument controlling calibration, and we have described that in the preamble, as well as specific practices, and if you think that in the final rule, we should be more explicit, and if you have some comments in that regard as to how that particular set of

requirements should be phrased to avoid ambiguity, if you think that is an issue, a comment in that regard would be useful.

MR. VARDON: Another questioner asks will the competency of analysts be tested and included as part of the CGMPs within the Training Section of the proposed rule, will there be proficiency training.

MS. STRAUSS: In our proposed rule? No, we have left to the manufacturer's discretion that particular training and experience requirement that would be appropriate for a particular position.

MR. VARDON: I have a number of questions about testing and I am going to save those questions until after Steve has spoken, so I hope you will bear with me.

Are dietary supplement manufacturers now required to conform to food GMPs, CFR-110?

MS. STRAUSS: They are basic sanitation requirements, so they should be following those.

MR. VARDON: Some CGMPs require that the organization of the Quality Control Unit be independent of manufacturing, i.e., report to a different vice president. Will you have such a requirement?

MS. STRAUSS: The requirements we have for Quality Control Unit are what we have specified. In the preamble, we talk about the makeup of the Quality Control Unit and that it can come from a variety of different areas of expertise within manufacturing, and we have not specifically said that it has to include any particular people or exclude any particular people or kinds of positions within a firm, so that really is a manufacturer's discretion.

MR. VARDON: Are maintenance records required?

MS. STRAUSS: Within the batch production record--and Sara will talk just a bit more about this--the maintenance and sanitation records for a particular piece of equipment used in producing a batch would be required to be kept within the batch, but as far as general facility maintenance records, we have not proposed requirements for them.

MR. VARDON: The proposed 111.20(d) requires plans to use equipment to control temperature and humidity. Is it acceptable to just monitor temperature and humidity in areas where it can be justified by scientific rationale, by

scientific rationale, that control is not needed?

MS. STRAUSS: The purpose of that requirement is to ensure that the dietary ingredients components, packaging and labeling don't deteriorate, and if there would be good scientific reasons for the controls to not require anything specific beyond the monitoring, if that is scientifically appropriate, then, that would meet what we have proposed.

MR. VARDON: This questioner asks about smooth, hard floors. Does the proposed rule require plans to be designed and constructed with smooth, hard floors, ceilings, and walls?

Is it acceptable for existing packaging areas that aren't smooth and hard to be protected in another manner, such as shield above the area that is exposed, and would FDA also agree that this isn't needed in areas where a product is fully contained, such as warehouses and secondary packaging?

Finally, for dietary ingredients where chemical processing occurs in closed tanks, why are smooth, hard ceilings necessary across the whole facility rather than just over the charging area?

MS. STRAUSS: That question raises a

number of points. We have proposed some general requirements for the facilities. If, in a particular situation, a commenter feels that what we have proposed needs to be reworded in a way, or needs to be adjusted in a way, or revised in a way to meet some circumstances that would require something different than we propose, a comment to that regard that would describe the situation and what would be a better wording, a better proposal, those kinds of things would be welcome.

MR. VARDON: I will ask one more question for this round, but I am saving everybody's questions, and as each speaker speaks, I will have these in reserve, and we will get to all the questions, I hope, by the end of the morning.

In Section 111.5, initials of operations personnel are specified, whereas, signature is required from 2(c) personnel. Why is there a difference? The initials of the operators, I guess, are specified for the people actually doing the operations, while the signature is required for 2(c) personnel.

MS. STRAUSS: I think what they are referring to is, say, in a batch production, if certain steps are completed, we said that the

initials of the person doing that particular step and the date that the step was performed to be recorded in the batch record, and then more of a signature is the Quality Control Unit.

I think just kind of the difference between someone doing a particular step versus approving the whole batch, we want to be sure that you kind of have more of a record of the full name.

If you think that that makes a difference, that the final rule should say initials for all or signatures for all, those comments are certainly something that we will consider like all of them. Is that it?

MR. VARDON: For right now.

MS. STRAUSS: I will reintroduce Sara in my efforts to avoid those questions.

As I mentioned, Sara was really very helpful to us in preparing the proposal, and she really was very well trained in botany and was very helpful to us because of her experience as an inspector, also had a perspective on the production and process controls that we are proposing.

She graciously agreed to help us in this regard, and I will now turn it over to Sara.

Proposed Production and Process Controls

MS. ACOSTA: Hi. I am going to discuss the production and process controls portion of the proposed regulations. The first thing is that the proposed regulations would require that the manufacturer have a system of production and process controls.

The purpose of the control system would be to ensure that the dietary ingredients or dietary supplements are manufactured, packaged, and held in a manner that would prevent adulteration, and this is the goal, to prevent adulteration.

The production and process control system would be required to be reviewed and approved by the Quality Control Unit. That production and process control system would include that Quality Control Unit and would also include the manufacturing operations including the laboratory operation, and holding and distributing, and finally recordkeeping, so the Quality Control Unit is going to be the umbrella for all those things.

The system of production and process controls is going to include the specifications, the testing that is going to ensure that the specifications are met, the monitoring material review, and disposition decision, and this is I

guess the big part or the biggest difference between the current and proposed regulations, that the manufacturer is going to be required to use master manufacturing records and batch production records.

So, where are these specifications going to be required? In very general terms, they are going to be required anyplace that control is necessary to prevent adulteration.

Examples are if it's heating steps or if there is drying times or cooling steps that is something that would prevent adulteration, then, you need specification for that, anything that a manufacturer identifies as the part that is going to control adulteration, then, that specification is going to be needed for that.

In addition, the proposed regulations identify areas that we would require that specifications are provided. That would be for the identity, purity, quality, strength, and composition of the incoming components. I am going to define that a little bit later, but the incoming components would include the dietary ingredients, ingredients and other substances that are used to manufacture, but don't remain in the final product,

and I will go back to that.

The specifications would be required in process where control is necessary for the final product and for packaging and labels. I am going to go back and define a little bit some of these terms.

We are going to define the term "component" to mean any substance intended for use in the manufacture of the dietary ingredient or dietary supplement including those substances that may not appear in the finished dietary ingredient or dietary supplement.

As I said before, a solvent is an example of a component that may not appear in the finished product. The components include ingredients and dietary ingredients, and the definition for dietary ingredient is the one that is in Chapter 2 of the Food, Drug, and Cosmetic Act, Definition 201(ff).

Ingredient is any substance that is used in the manufacture of the dietary ingredient or dietary supplement that is intended to be present in the finished dietary ingredient or dietary supplement.

It includes, but it is not necessarily limited to, the things that are mentioned in that

Definition 201(ff) of the Food, Drug, and Cosmetic Act--and in a few slides after this I am going to go into more detail--and other substances, any substance that is not a dietary ingredient within the meaning of that Section 201(ff) and that when used, it is reasonably expected to become a component or otherwise affect the characteristics of the dietary ingredient or dietary supplements should be either an approved food additive or generally recognized as safe.

So, what specifications would be needed for packaging and labels? The packaging and labels for dietary ingredients or dietary supplements should be safe and suitable for the intended use, should comply with all other applicable statutory regulatory requirements, and should not be reactive or absorptive to affect the dietary ingredient or dietary supplement.

The packaging must protect the dietary ingredients from contamination and from deterioration.

What else will a manufacturer be required to do? The manufacturer will be required to monitor the process to ensure specifications are met and detect any unanticipated occurrence. There

should be a material review and disposition decisions on different occasions.

Anytime that a specification is not met or there is an unanticipated occurrence that may lead to adulteration, you are going to limit your review and disposition decisions.

If a master manufacturing record set is not completed, you also need to do this. If an instrument or a controlled calibration suggests a problem, you are going to review, and if a dietary ingredient or dietary supplement is returned to the manufacturer because it has any problem, then, you are going to do a material review and disposition decision.

In addition to that material review and disposition decision, there should be documentation of what actions are going to be documented. When this happens, you are going to identify the specific deviation or an anticipated occurrence that you are investigating.

You are going to describe that investigation. You are going to evaluate whether or not this deviation or unanticipated occurrence resulted in or could lead to adulteration, identify the actions taken, and show that the Quality

Control Unit approved the material disposition decision.

The manufacturer would be required to have a Quality Control Unit, and this is one or more persons, we are not specifying the number of persons, that would approve or reject procedures, specifications, controls, test, and deviations, or modifications from any of these, approve or reject materials that are received and products manufactured, packaged, and labeled by the firm, and review and approve the master manufacturing and the batch production records.

In addition, an appropriately trained person in the Quality Control Unit would be required to review CGMP-related consumer complaints to determine if there is a quality problem in a particular product. In addition, they would be required to investigate any CGMP-related consumer quality complaints when possible relationships exist between the dietary supplement quality and the reported adverse events.

The manufacturer would be required to keep CGMP-related consumer complaint records, and we recommend, but would not require, that a manufacturer report serious adverse events to the

FDA.

So, what seem to be in the master manufacturing record? The manufacturer needs to prepare and follow this recipe or master manufacturing record, and that recipe is going to include lists of components and as I mentioned before, components are either dietary ingredients, other ingredients, or substances that don't appear in the finished product, and here is where I am going to go, and this is almost directly quoted from the Food, Drug, and Cosmetic Act, Section 201(ff).

A dietary ingredient is a vitamin, a mineral, an herb or other botanical, an amino acid, or, and I struggled to get this sentence out, but it's a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any of the above. So, this is the definition that is directly in the Food, Drug, and Cosmetic Act.

Continuing with the master manufacturing record, it is going to need specifications for controls necessary to prevent adulteration. Remember this is the key word for everything that I

have been saying, it is preventing adulteration.

It is going to include the weight and measure for each component. Remember the master manufacturing record is like a recipe, so as with any recipe, it includes the weight and measure for each of the components, and as with any recipe, instructions for adding, mixing, sampling, and testing.

It is going to include expected yield, specifications for the packaging and labels that are to be used with this product, and the manufacturer is going to be required to keep the master manufacturing records.

So, once you have that master manufacturing record, what are you going to do with it? You are going to use it to create batch production records. The batch production record is going to accurately follow the master manufacturing record. It is going to just mirror that record.

The Quality Control Unit is going to review and approve each batch production record. It is going to be cross-referenced with receiving and batch production record. It is going to include material review and disposition decisions, any instances where reprocessing is needed, and it is

going to include the release for distribution of any batch. The records will be required to be maintained for three years beyond the date of the batch production.

So, what other things are going to be included in that batch production record? It is going to include, in part, the batch lot or control number for the product, the identity of the equipment and processing lines used, and this next item goes back to the question that was read earlier.

The batch production record is going to include the date and time of the maintenance, cleaning, and sanitizing of the equipment, and processing lines that were used, the incoming shipment lot is identifier, and the identity and weight or measure of each component used.

The record is also going to include the dates and initials of the persons completing and verifying the steps, the date the batch was produced, the actual test results for any testing performed during the batch production, any material review and disposition decision, documentation that the final product specifications are met, and copies of any container labels used and the results

of examinations conducted during labeling operations to ensure that the containers have the correct label.

The signature of the Quality Control Unit would be required to document the batch production record review and any approval for reprocessing or repackaging.

These manufacturing operations proposed are similar to those in Part 110, the umbrella food CGMP. The manufacturer would be required to design or select equipment to ensure that the specifications are achieved, conduct manufacturing operations in accordance with sanitation principles, and take precautions to prevent contamination.

This is my last slide. The precautions to prevent contamination would include protecting against growth of microorganisms and potential for contamination, washing or cleaning components that contain soil or other contaminants, preventing the growth of microorganisms and decomposition by methods, such as sterilizing, pasteurizing, freezing, refrigerating, controlling pH, humidity or water activity, preventing against inclusion of foreign material by using filters, traps, magnets

or electronic metal detectors, identifying all processing lines and major equipment used during manufacturing to indicate their content, the batch or lot number and, when necessary, the phase of manufacturing.

Questions?

MR. VARDON: I have many questions.

Will the manufacturer be expected to perform process validations or will in-process testing suffice, and what level of in-process testing will be expected in lieu of process validation data?

MS. ACOSTA: I think I will probably have Karen answer that question.

MS. STRAUSS: We haven't proposed requirements for process validation.

MR. VARDON: This questioner asks about specifications for botanicals. For botanicals used in simple hydro-alcoholic extracts where no marker claim is made or for use in a tea mixture, what is the meaning of strength or composition?

MS. ACOSTA: These are not fixed definitions. These are interpretations of identity, purity, quality, strength, and composition, so let me just briefly go over those

and maybe that will clarify that.

In the case of identity, what we interpret that is that what is represented to be on the label, the purity is without impurities, and that is the desired product. Quality includes the identity, purity, and strength for the intended purpose.

Strength is the concentration or the amount intended for unit of use. Composition is the intended mix of product and product-related substances.

In terms of strength, I don't know, maybe Karen can talk a little bit more about this, but I would figure if you say in a label that this has so much of this, then, your product should have so much of that.

In terms of the tea that is going to be performed, extracted by the consumer, that would be more of a --

MS. STRAUSS: The label should give the directions for use, and within the directions for use, there would be quantity per serving or quantity per dose or whatever, whether it is made into a tea or used as a tablet.

So, the principle is the same, how that

consumer would use that product per dose, per serving.

MR. VARDON: The proposal also requires packaging that contacts dietary ingredients and supplements to not be reactive or absorptive, and this implies stability, but the proposal requires no stability testing.

Therefore, please clarify the intent of the statement and what is required.

MS. STRAUSS: One is referring to the dietary supplement itself and another is the packaging, I mean there are two different concepts, and stability in the packaging relates to the material that is used in the packaging, so that it doesn't affect the dietary supplement product.

MR. VARDON: Who can one contact to determine the GRAS or food additive status of an ingredient that is commonly used in the food industry? Shellac is used in confectionery products, but it is used as an inactive ingredient, is not codified in the CFR, nor is it listed in the UFAS database. I am not sure what that is.

MS. STRAUSS: I would relate to the CFR for those materials that are GRAS or food additives, and also there is a web site that the

Center has on food additive safety that one could reference for those that are already GRAS.

MR. VARDON: Do the proposed CGMPs require equipment cleaning and maintenance information including time and date of cleaning be included in the production batch record?

This information is ordinarily contained in equipment logbooks. Would this requirement supersede logbooks or be an addition to logbooks, or could the use of logbooks eliminate this requirement in the batch record?

MS. STRAUSS: As we proposed it, it would need to be in the batch record. It wouldn't prevent someone from keeping a logbook, but as we have proposed it, that information would need to be in the batch record.

MR. VARDON: Will a vitamin formula which requires a prescription fall under the drug CFR or the proposed CGMPs for dietary ingredients and supplements?

MS. STRAUSS: If it's a prescription, it would be a drug.

MR. VARDON: Is the manufacturer allowed to use vendor certificates documentation to demonstrate that the product meets the established

specifications, and then spot check when necessary, or is it possible, or must all testing be completed by the manufacturer or contractor?

MS. STRAUSS: I will refer you back to the slide that we showed of kind of the schematic, and Steve will talk more about testing. If a Certificate of Analysis is received and final product testing is performed, that would be acceptable.

If final product testing cannot be done because there is not a method available, that Certificate of Analysis could not substitute for the testing of in-process, because somewhere along the way, material needs to be confirmed that it is, in fact, within the product either at the end or at the beginning and the middle, so it depends on when that C of A is looked at.

If you are doing final product testing, there is nothing that prohibits the C of A from being used for incoming, but if incoming testing is required, you can't do finished product testing, then, the C of A would not be appropriate. In fact, the situation where Digitalis was misidentified as plantain, and there was a C of A that said it was plantain, but it really wasn't.

So, if we need testing to confirm the label contents at incoming, you can't do final product, then, it is not appropriate.

MR. VARDON: This questioner asks about production and process controls, and why did you not require an SOP, a written SOP to provide for consistency and continuity?

MS. STRAUSS: We didn't require any SOPs to lessen the burden for industry, but we required the necessary records for traceback.

MR. VARDON: Given that expiration dating isn't required, if a manufacturer uses an expiration or "used by" date, does that constitute a claim that he can measure potency or efficacy at that point in time, and should they not be using dating if the active ingredient is not known?

MS. STRAUSS: We have not proposed expiration dating and we have not prohibited expiration dating. If expiration dating is used, in the preamble we discuss that and interpret that if you are using an expiration date or "best if used by" date, there should be data to support that date.

MR. VARDON: If the manufacturer isn't required to report adverse events, what body

manages the capturing, recording, and reporting of adverse events?

MS. STRAUSS: There is a body within CFSAN and Med Watch that capture the events that are reported to FDA.

MR. VARDON: How will safety signals or adverse events, will they be required to be in the label, I guess as a warning?

MS. STRAUSS: No, we haven't changed any label requirements by this proposal.

MR. VARDON: I should tell you if I mischaracterize your question, we will give you an opportunity at the end to reask it.

This questioner asks about the Quality Control Unit. Is the Quality Control Unit responsible for releasing the product specifications, and is the quality testing the analyst's responsibility?

I guess maybe if you can describe again what the Quality Control Unit's responsibilities are.

MS. ACOSTA: The Quality Control Unit does approve or reject procedures, specifications that controls the tests, and any deviations, so they would -- the answer is yes to the question.

MR. VARDON: The proposal requires that you determine the suitability of your equipment, either equipment must be capable of operating satisfactorily within the operation limits required by the process and that the equipment must function as intended.

This implies that the equipment installation and operational qualification verification and some level of performance qualification verification, however, the proposed rule states FDA is not proposing verification requirements.

Please clarify, if possible, with detailed examples now the intent that must be met without verification.

MS. STRAUSS: We have proposed it in the way that we have proposed it by saying that you must ensure that it performs as intended, that the manufacturer has discretion to ensure in whatever manner is appropriate that the machine works as intended.

Validation and verification requirements is a process that is well described both in guidance documents, for example, for food equipment that is automated, so there is a process that is

pretty well defined, and we have not proposed validation, but by using the phrase that it functions as intended, that leads to the manufacturer's discretion how that is determined. We are clear that we have not proposed validation or verification of equipment used.

MR. VARDON: This proposal requires that the laboratory take samples of each batch of packaged labeled product to ensure that the proper label is used. Is that not better suited to the QC Unit employee taking regular samples during the packaging process?

MS. STRAUSS: I believe we propose that as a responsibility and authority of the Quality Control Unit, and we haven't said who would do that.

I mean there are some things that would be under the Quality Control Unit, responsibilities that could be done by, say, someone in the process of manufacturing, you know, actually doing that batch production as part of master manufacture record gives instructions on sampling and the person running the machine samples. That would be appropriate, but it would still be under the umbrella of responsibility and bodies of the

Quality Control Unit.

MR. VARDON: I have actually got a couple of short questions, so maybe we can do two more.

Should the Quality Control Unit, one or more persons be an employee of the manufacturer, or may the unit be outside, a third party?

MS. STRAUSS: It could be a contractor, but then it would be someone that would have the oversight of the manufacturer, so we haven't said that that necessarily has to be someone in-house.

MR. VARDON: Will a manufacturer be required to provide a Certificate of Analysis if requested by the federal agency, such as FDA or NIH?

MS. STRAUSS: We haven't proposed a requirement for that.

MR. VARDON: It is 10:25 according to my clock and it is time for a break. Why don't we meet back here in 15 minutes and I think that will be in time for Steve's presentation.

[Break.]

MS. STRAUSS: I would like to start by introducing Dr. Steve Musser. He is the Lead Scientist for Chemistry in the Center for Food Safety and Applied Nutrition. He is also Chief of

the Instrumentation and Biophysics Branch, Office of Scientific Analysis and Support, here at CFSAN.

He is responsible for developing specialized analytical methods for a number of CFSAN program areas including dietary supplements, food contamination, and natural toxins. He has published numerous articles and regularly speaks on these research topics at national and international scientific meetings.

He is an expert on analytical instrumentation and has a well-established professional reputation in the areas of analytical chemistry. He has a Ph.D. in medicinal chemistry and served as a research fellow at the National Institutes of Health before coming to FDA as a research chemist in 1991.

Steve.

Proposed Laboratory Operations

DR. MUSSER: Thank you, Karen.

I would like to talk about laboratory operations now. This is a very small portion of the regulation, but one that we have received quite a number of questions on. I am going to try to clarify a little bit of that, but I know that there will be some additional questions as there always

are on this particular portion of the proposed rule.

The laboratory operations part of the regulation is divided into three separate parts, that you must establish and follow laboratory controls, that you use adequate facilities in-house or from outside sources to perform testing and examination.

That means if you don't want to set up your own analytical shop inside your business, you can contract that out outside, but then you would have to verify the testing and the results used by your contractor, and finally, that you keep the laboratory test and examination records.

So, you have basically established the specification and now you have to keep the results from the testing that shows that you have met those specifications.

Within the establishment and following of laboratory controls for testing, there are two basic components that will be followed throughout this particular portion of the presentation.

You will notice that you may either test the finished product, if you have a test which is capable of measuring all the specifications for

that particular product and one final test, then, you can test the finished product.

If you can't test the finished product, then, you should process to the next three, which are testing the components, the dietary ingredients, and dietary supplements that might be received, as well as in-process materials as specified in the master manufacturing record, and if you are using water in any way, to ensure that it meets EPA national drinking water regulations.

Now, in the food code, it is not specified that we use EPA national drinking water regulations, but we felt that this was a clarification and gave people trying to comply with this particular rule an idea of what we meant when we talked about using water that is in the food code that is safe and well characterized.

Laboratory operations then for actual testing, you can test the finished batch of dietary ingredient or dietary supplement to ensure the identity, purity, quality, strength, and composition of that particular finished product.

If there is no scientifically valid analytical method available for testing the finished batch--and I will talk a little bit more

about what we mean by validated method--available for the finished batch, then, you would need to test the incoming components of dietary ingredients or dietary supplements to determine whether the specifications have been met and test in-process in accordance with the master manufacturing record to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements.

Now, basically, what this means is that you are testing everything, so if, for example, you have established a supplier that you wish to use for a dietary ingredient, they have given you some product, you have seen that it met your specifications, whatever those specifications are, you are now going to be receiving that product on a routine basis.

You can't just take that original test as your test for quality, purity, strength, and identity. You would have to test each batch. You can't skip individual lots that are going to be used for the manufacture.

You would have to test each individual lot to see that it met your specific requirements, and those requirements are what you specify, not what

the FDA specifies. You know your product best, you specify what those particular criteria are that must be met in the original part of establishing your controls.

So, what types of tests are we recommending that you perform? Those would be tests for types of contaminations that may adulterate the product, and they might be filth, insects, or other extraneous material like glass or metal parts, bacterial or microorganisms contamination and toxic substances.

Toxic substances could be inorganic compounds, organic compounds, or if there is a historical precedent for particularly in botanicals for one plant being mistaken for another plant where one is very toxic and the other is not, you might then want to have a test for known toxic substances that are commonly confused.

Again, the manufacturer decides what tests to perform and the specifications that must be met by those tests.

The test must examine or use at least one of the following tests - organoleptic analysis, microscopic analysis, chemical, or any other test that the manufacturer feels is appropriate to meet

their specification.

I would like to make a clarification here because this really hasn't been clear in a number of the questions that we have gotten. We are saying at least one, so let me give you an example of where you wouldn't want to use just one.

Let's say, for example, you have a raw botanical product, that the leaves and stems and all parts that might be needed for its identification could be identified simply by looking at the product and possibly by an organoleptic analysis of that particular plant.

If you had a qualified, trained botanist that, you know, you had a documented procedure for what criteria you are going to use to identify this particular plant, then, perhaps one test would be good enough.

If, on the other hand, that product came in as a ground product which could not be identified, which would have no characteristics other than a particular taste, you may want to use another test in combination with organoleptic testing to ensure that you have what is claimed to have been provided by the supplier.

Establishing and following laboratory

controls. This is where we have really gotten into a lot of confusion into what exactly we mean by valid methods and validated methods and use of validated methods.

The proposed rule says that you must select and use scientifically valid methods. FDA interprets this to mean that the test is appropriate. That means that if you are testing for water, your test should be appropriate for testing for water, and not soil, but these are commonly understood measurements, and that the method is validated.

What we are providing here are some sources of validated methods. They might be obtained from AOAC, from USP, or another international standard, from a peer-reviewed journal, or they can be generated in-house by internationally accepted guidelines, such as ISO-17025.

Regardless of where the method comes from, you can't just pluck it off of some Internet site or some book and use it directly. You must validate the method in your laboratory or in your particular facility.

You must demonstrate that the method

conforms to the specifications which you have identified for that product and that the test works according to those specifications in your laboratory.

What we are providing here in this particular case is just a source of some possible places that you might find methods that you can use to meet the criteria that you have specified for your particular product.

Finally, you need to keep the results of these records. In other words, you have got a particular criteria. Let's say that you have to have a certain component that has to be present at 10 parts per 1,000, and you have got a method for measuring this, you have validated the method.

Now, you would need to actually perform the testing and keep the records that you have met those specifications in the record.

So, that would be for the finished product if your test is for finished products only, or the components, once again, the components, the dietary ingredients, or the dietary supplements received and in-process materials that might be used in the master manufacturing record, and if you are using water, again, that it meets the EPA primary

drinking water requirements.

That is really just a summary or a small explanation of a number of the issues that we have already gotten questions on this proposed rule. I know that it is much shorter than a lot of the other presentations, but there has been a lot of interest.

I hope that this clarifies some of the questions that you might have on our interpretation or the way we have written the rule.

Thank you.

MR. VARDON: Thanks, Steve.

I do have questions already about testing, so I will begin asking them.

If Certificates of Analysis aren't sufficient, this questioner asks, must he test for alcohol and water, which are two of the ingredients in hydroelectric processes for producing of botanicals?

DR. MUSSER: Would you read that question again, please.

MR. VARDON: Yes. If Certificates of Analysis aren't sufficient, this questioner asks, must they test for alcohol and water?

DR. MUSSER: That is kind of a two-part

question, and I would like to clarify Certificates of Analysis, because Certificates of Analysis can mean a lot of things, and in some cases they might be appropriate and in some cases they might not be appropriate.

So, for example, let's say that all of your testing is done by the particular supplier, which is fine. Let's say you are the final manufacturer, you have got a supplier. You specify to them that they must conform to these specifications.

Your Quality Assurance Unit goes to the site. The Quality Assurance Unit assures that the tests are being run correctly and that the test report or what they call their Certificate of Analysis meets all of your specifications and you have inspected them to make sure that they are adhering to those requirements.

That is quite a different thing than if you never go to the supplier's site and you just accept what they provide you as having met their specifications.

So, it's the same C of A, but two completely different things because, in one case, you have gone there and verified that the supplier

has met your specifications, in the other case, you are accepting their word in total.

A fine point of clarification, but a very serious one.

The second part of that question had to deal with the particular contaminant that might be present in water. If that contaminant were above EPA's recommended level for safe water quality, then, of course, you would want to test for that particular component and make sure that the water did meet those specific guidelines.

MS. STRAUSS: Let me just kind of reiterate what Steve has said. When he talked about the Certificate of Analysis that comes from a supplier that you have determined to be reliable, that is just like an outside lab.

You are relying on them to do that test for every single incoming, not that they test now and again, but just like you would send it to an outside lab, if you are relying on it for all of the specifications, it would need to be that outside lab or that outside manufacturer would need to be testing for everything that is on that C of A, not just now and again.

MR. VARDON: This question also regards

the C of A. If a manufacturer uses a Certificate of Analysis on an ingredient to assure compliance with the test, such as a test for aflatoxins, he must also test the finished product, the finished batch for aflatoxins also. Is this correct?

DR. MUSSER: Let me see if I can put this in a slightly different perspective. Let's say, for example, that you were producing a product with only one ingredient in it, no other ingredients, just one powdered ingredient that you put in a capsule.

Part of your specifications for that product were, let's say it's a ginseng product and you have specified--no, let's say it's a vitamin, let's say it's vitamin C, for example, and you have specified that there be X amount of vitamin C, and your test method is for vitamin C.

That test for the finished product would also have to be capable of determining the amount of aflatoxin which is a mold contaminant that would be present in that product, as well.

If you couldn't test for the aflatoxin, as well as the component in your finished product, then, you would have to do all of the individual component testing as it came in, so you would be

looking at a test for contamination of aflatoxin in this particular product.

You might have another test for the amount of the particular ingredient that you were using, and so on, and so forth, according to your specifications.

MR. VARDON: Will FDA allow the German pharmacopeia or pharmacopeial standards without validation?

DR. MUSSER: The way the rule is currently written, you must validate the method that you are using in-house or by your contractor. It must be validated for your particular purpose, and you may not take just the method--I mean that is a wonderful source of methods, it really is, but you would have to demonstrate that it met your particular performance criteria.

MR. VARDON: For EPA testing, what level and schedule of testing is required, how frequently?

DR. MUSSER: That's a good question and really one that I am not prepared to answer.

MS. STRAUSS: We haven't specified, we haven't required a periodicity of testing. We have just said that water must be tested. That would be

a good comment to give to us.

MR. VARDON: Do you have to confirm that alcohol is really alcohol and that distilled water is really distilled water and/or are organoleptic tests sufficient?

DR. MUSSER: In the case of distilled water, that would have to conform to the drinking water standard, which probably you couldn't meet EPA requirements for drinking water standards by organoleptic testing, although we leave that open for you to demonstrate otherwise.

The alcohol, you would have to test to be sure that it was ethyl alcohol, for example, and not isopropanol or that it wasn't contaminated with methanol or something such as that.

MS. STRAUSS: Concerning water, I would just like to add that the purpose of the requirement was to ensure that, say, if well water is used from a non-municipal source, that it also meets the drinking water regulations, but we don't prohibit using water of a higher quality than drinking water.

So, if a process needs distilled water or any other kind of more purified water, that is not prohibited.

MR. VARDON: Let's go to the next question. Here, the questioner asks in the event that there is no valid method for testing a particular finished product, and the requirement is to test incoming components, will the regulations allow for validation of a particular supplier, that you don't have to test each lot of incoming material except for periodic verification purposes.

DR. MUSSER: As the rule is currently written, you would be required to test each batch. You wouldn't be allowed to--or validate a manufacturer or supplier.

MR. VARDON: Did your answer regarding Certificates of Analysis imply that suppliers must be audited by the Quality Assurance function? Is this a requirement?

DR. MUSSER: If you are using that Certificate of Analysis to support your specifications for manufacturing, then, yes, the Quality Assurance Unit would have to audit that supplier and assure that the specifications and procedures used to provide that Certificate of Analysis have been met in accordance with the rules that you identified.

MS. STRAUSS: I will just reiterate again

that according to what we propose, you couldn't accept a Certificate of Analysis that wasn't substantiated by testing every single shipment lot that you receive, that the manufacturer or the supplier, it would be just the same as an outside lab that a firm would send their incoming shipment lot to be analyzed.

You would look at them both as comparable. I know from other tasks involving dietary supplements that Certificates of Analysis in this industry are problematic, the reliability is very questionable in many cases.

So, relying on a Certificate of Analysis for substantiating what is claimed on a label without being tested, an incoming lot is really not going to achieve what we want to achieve for consumers, so it is important that every product have testing to support the label claim.

MR. VARDON: Steve, in answer to a question, you said that you must validate methods in-house or words to that effect. Does that mean verify as opposed to validate for standard methods, such as AOAC or from other pharmacopeias?

DR. MUSSER: No, we mean validate, not verify. We mean that you actually perform the

precision and accuracy, validation of that particular method in your analytical laboratory or in whatever testing facility you have identified.

MR. VARDON: This questioner asks why does the proposed rule put tighter restrictions on the use of Certificates of Analysis for ingredients than is found in the drug GMPs.

DR. MUSSER: In fact, it is identical to drug GMPs in that regard.

MR. VARDON: Many companies buy solid dosage and other forms for the purpose of repackaging, and the bulk product isn't subjected to further processing, it is only repackaged.

Can that manufacturer or repackager accept the vendor Certificate of Analysis or do they have to test the product after bottling or repackaging?

MS. STRAUSS: I included this in my presentation. A packager or labeler is not out of the loop as far as CGMPs are concerned. They need to ensure that what is in the package, in that container, is actually what it says on the label.

We have not said how that packager or labeler would ensure that that product in the package conforms to the label. We have left that to the manufacturer's discretion, but they clearly

are responsible for what is in the package.

If we need to be more detailed in our final rule, we may learn that through comments, but at this point, they are not out of the CGMP loop.

DR. MUSSER: I should take this opportunity to point out that just by asking us questions here and responding may not get your particular issue or question in to us and considered for the final rule.

So, even though we may give you an appropriate answer, if you feel that the rule, as it is currently written, is not clear enough or needs additional clarity, please provide us with that comment as a written record.

MR. VARDON: Steve, validation as used by FDA means that the process is documented. Will this documentation be subject to FDA review?

DR. MUSSER: Yes, it would be.

MR. VARDON: This questioner states that their product is a peppermint extract, and one provision states that they must establish a specification for strength and composition. What does this mean for their product peppermint extract? Must they establish a spec for methanol?

DR. MUSSER: Menthol or methanol?

MR. VARDON: Menthol, I am sorry.

DR. MUSSER: Thank you, a little different.

When we wrote this rule, we tried to allow the manufacturer as much control over their particular product as possible. If you felt that menthol was a critical ingredient in that particular extract and that you were controlling that, or if you were putting, let's say, for example, you put 5 percent menthol or 1 percent menthol on the label of your particular product, then, that would probably be a specification that you would want to meet.

So, yes, then, you would have to test for it. If it's part of 20 other products or 20 other components, and you think that there is some other component that is within that extract that is more important for your particular criteria, then, that would be the specification that you wrote, but you would have to have some specification for that particular component in that case.

I realize that these are very fine differences and probably why there is the confusion, but we had to allow a lot of flexibility in the rule to encompass all of the particular

products that would be regulated under it.

MR. VARDON: Can organoleptic tests be used for evaluating microbial levels, i.e., can one remove any darkened leaves and make sure you are only using vibrant botanicals?

DR. MUSSER: The key here is that you would have to validate that particular test. Let's say there is a particular coliform specification that you have identified in your particular product. You would have to demonstrate that by your organoleptic means, you were capable of consistently meeting that particular requirement.

If you couldn't demonstrate that you were able to meet that particular requirement using an organoleptic test, then, it wouldn't be appropriate and it wouldn't be valid, and therefore, it would fail the criteria for use in the rule.

MR. VARDON: A related questioner asks why require each manufacturer to validate methods that have already been validated by USP, AOAC, et cetera. Parts of their initial validations would include inter-laboratory analysis already.

Is this in keeping with the food GMPs?

DR. MUSSER: We feel that it is. In addition, we feel that simply because a method

works in one laboratory, is not going to mean that it works in another laboratory, and we have a lot of documentation to show that this is indeed the case.

That is why we are requiring that methods be validated in the laboratory for which they are going to be used.

MR. VARDON: Let's make this the last question for this section. I recognize there is still many more questions about testing, and we can get to those later.

Karen talks about meeting the label, the label's stated amount. Usually, there are no label claims for excipients. Must you test for the spec amounts of all components in the supplement?

MS. STRAUSS: Yes, if it's final product testing, you would want to be sure that the excipients that were used were the ones that were intended to be used by the master manufacturing record. If not tested at the final product stage, they would need to be tested as an incoming.

DR. MUSSER: If I can just clarify because I think the questioner might have meant something a little bit different. In addition to what Karen states, if the label claim says, for example, you

are using methyl cellulose as a binder in a tableting process, and you don't specify on the label that there is 5 percent methyl cellulose, then, you don't have to verify that that is meeting that particular label claim.

Alternatively, if the specification in your master manufacturing record says it must be 5 percent methyl cellulose, then, you should have some method of showing that you have met that master manufacturing record, another part of clarity of this.

Public Comment Period and Next Steps

MS. STRAUSS: The last part of my discussion relates to the comment period and the kind of comments that are useful in looking at the various requirements.

Throughout the preamble, we have asked for comments on many, many issues, and we have, in that highlight section, focused on certain issues that we in particular want comments on.

For example, we have requested comment on whether there should be certain additional personnel records. That would be, for example, records of consultants, records of training of various personnel. We have also asked for comment

on whether there should be written procedures.

As I mentioned earlier, we have not required this because we wanted to lessen the burden on industry, but this is an area we have asked for specific comment on.

Equipment verification or validation, process validation. The only validation that we have required is of the laboratory method in the laboratory operation portion of the proposal, but we also would like comment on whether there should be specific verification or validation requirements for automatic electronic or mechanical equipment.

Expiration dating, we have asked for a specific comment on that, and also on animal-derived dietary ingredients. There are some special concerns with regard to certain infective diseases especially VSC kinds of things that we want to know whether we should have some special requirements for animal-derived dietary ingredients. There is considerable discussion in the preamble about this, so I would refer you there if you have any more particular questions about what this relates to.

We have also included an exemption for those persons who handle raw agricultural

commodities. This parallels the food CGMP, which would exempt just the people who handle, who harvest, transport that raw agricultural commodity. We wonder if this kind of an exemption should be maintained in a final rule.

For a comment to be really useful to us, we want to know specifically the requirement that should be included or dropped from the requirement, and then in the absence of that comment, tell us how we could still ensure the identity, purity, quality, strength, and composition of the dietary ingredient, how we could ensure that the dietary ingredient or dietary supplement is not adulterated in the absence of that requirement, or how we could efficiently enforce the rule if we were not to include that particular requirement.

So, both the requirement and the whys, the whats and the whys are very important. Many of the questions deal with clarity. If you have asked a question about clarity, and you think that if we include some additional information that would help to clarify something that is now ambiguous, let us know what that would be, as well.

I would just kind of reiterate that the 90-day comment period after publication ends June

11th and that the comments should go to the Dockets Management Branch, and the two addresses are given here.

Visually, here are the post-publication outreach meetings that we have planned, and for additional information, you can get that at the CFSAN web site.

I think we have left a little bit of time on the agenda for questions on this section, although maybe there won't be any and we can move on.

MR. VARDON: Well, actually, we didn't, but my experience in these forums is that most of the questions relate to testing. What I was going to say is that at the end of my presentation, if there aren't many questions about economics, we can turn it over to the remainder of the questions about testing and other things.

Someone does ask could you provide a ballpark estimate of when you expect the final rule to be published.

MS. STRAUSS: Good question. The next steps in getting to publication are when the comment period closes, we will look at all of the comments that have been submitted to the docket.

That is why it is real important that you made a comment here, asked a question, you want clarification, that you send that to the docket, because we look at every comment, analyze every comment that is in the docket.

Then, we rewrite the proposal. Then, it goes through the same clearance, rewrite the final rule, and it goes through the same clearance process as did the proposed rule. On a good day, I would suggest that it would be done, that we would have a final rule within the next year, but suggestions are often just that.

MR. VARDON: We do have a couple more questions related to that.

In light of the length and complexity of the proposed rule, will FDA provide an extension of the comment period, about a three-month extension, and has the Agency already received a request for the extension?

MS. STRAUSS: It is my understanding that there was a request for an extension of the comment and it is under consideration. I am operating under the assumption that there will not be an extension, for me, in my role, that is what I need to do until the determination is made.

At this time, Peter will give discussion and further information on the analysis of economic impacts.

I introduced Peter earlier. He is our economist, was the lead writer on that particular section of our proposal.

Economic Impact Analysis

MR. VARDON: Thank you, Karen.

There was a large staff of economists and epidemiologists that conducted this analysis, and we conducted our analysis in accordance with Executive Order 12-866, which requires an assessment of all the costs and benefits.

From that assessment, we are required to select the regulatory approach that maximizes net benefits. We determined in our economic analysis that the rule, if adopted as it is, would be significant, which means that it would have an impact of more than $100 million on the economy, but we think it will have a significant impact above that $100 million.

We also think it will have a significant impact on small businesses, so we looked at regulatory options for those small businesses.

We felt the economic rationale for the

proposed rule is that there is a market failure, consumers can't take control of their choices because there are hidden defects, so there is the potential for hidden defects as it is, and private incentives aren't sufficient to adopt adequate preventative controls. This is because controls today are costly and voluntary, and those who adopt preventative controls would be at a competitive disadvantage if everyone doesn't adopt them.

Consumers can't distinguish between those manufacturers that adopt preventative controls and those that don't. So, consumers would be at a disadvantage also.

We looked at regulatory options. The first option we looked at was no new regulatory option, but in a survey we conducted in 1999, and many of you might have participated in that survey, we found that 48 percent of very small firms and even 11 percent of large firms don't follow any GMP model, so they are indicating to us that they are not following a full range of preventative controls now, so we didn't feel that was an ideal regulatory option.

We also looked at fewer requirements for vitamin and mineral manufacturers. We felt that

might be a viable alternative, if plant and animal-derived dietary supplements have greater variation in product quality than synthetically-derived products, then possibly you could find a rationale for having more requirements for those plant and animal-derived dietary supplements.

The advantage of such a requirement is that fewer products and firms would be affected, so the total compliance costs would be less, but the disadvantage is that we don't have any evidence at all that there is a difference in health risk between synthetic and naturally manufactured ingredients.

We also looked at more restrictive regulations than what we are proposing, such as product quality testing for each incoming shipment lot in addition to the final product testing, and mandatory written procedures for each provision, but we felt there were disadvantages that it is costly and difficult to link to health benefits.

We looked at HACCP without the other elements of the CGMPs, and the advantage is that the manufacturers themselves could determine how best they could eliminate or control the hazards,

but we felt the disadvantage is that it wouldn't create uniform minimum product quality across the industry and there are significant benefits that consumers have with a certain knowledge that they are minimum uniform quality standards.

We also looked at final product testing only, but the disadvantage we felt was that not every finished product has a test that confirms identity, purity, quality, strength, and composition, and also finished product testing couldn't ensure the discovery of all contaminants, such as when there are hot spots, in other words, there could be false negatives.

We looked at the sixth regulatory option just regulating high-risk products or high-risk hazards, but the disadvantage is that we don't know what those high-risk products or hazards are. There is significant under-reporting and what is reported may not be linked with the actual risks or the highest risks, so we didn't feel that was a tenable alternative.

As I mentioned, we conducted a survey of the industry in 1999 of those firms that would be covered by this rule, and we developed a database of firms derived from several sources.

We have FDA's official establishment inventory, and we used a database that was supplied by various trade organizations, and there were electronic databases, such as Info USA that we used, and we collated all those firms and determined that there are about 1,566 firms that would be covered specifically in this industry at the time the survey was conducted in 1999.

Those covered firms are firms that manufacture, package dietary ingredient suppliers, repackers, and holders. We found that most firms are manufacturers, no surprise there, and that most firms are small, as classified by the Small Business Administration, which means there are 500 or fewer employees.

We sent our survey to about 966 firms on our database, and we received 240 responses.

From industry sources also, we know that the consumer use is growing and there is a significant growth in the dietary supplement industry, so there are very large competitive pressures out there.

The growth rate has been about 10 percent per year for the last decade, and the per capita consumption, the number of units per U.S. resident,

as we measured as the number of units per U.S. resident, has grown also, about 3 percent per year.

So, the total industry size has grown, it has grown, it has grown, and the sales from a couple of years ago were about $15 billion.

From our survey, we learned, well, first, let me say that we stratified our survey by product type and size. The product type we use were those who manufacture vitamins and minerals as their primary product, those who manufacture or pre-package botanicals and herbals, and those who manufacture amino acids, proteins, and animal extracts and others, and we stratified by size also.

We looked at large firms, we stratified by size of employees, so large firms with 500 or more employees was one strata, looked at small firms, which we identified as those between 20 employees and 500 employees, and we created our own strata called the very small firms, which are those firms with 20 or fewer employees.

We did that because this industry is characterized by very small producers. The median manufacturer has 8 employees, and 90 percent of all firms are small as defined by the Small Business

Administration, so we wanted to take a careful look at the very small manufacturers.

We also had a strata of those who we just didn't have much information about. We knew they manufactured something. So, we had a strata of unknowns, which were about 17 percent of the industry.

From our survey, we also determined that there is very large turnover in this industry, about 17 percent enter the industry and about 17 percent leave the industry every year.

We found from our survey that many of them don't follow any model, any GMP model, and that was a clear signal to us that there is some real need for this kind of rule.

We felt that the consumer benefits from this kind of rule are that there would be better consumer health, which we felt would mean that there would be a lower risk of contamination and misbranding, there would be a reduced risk of glass fragments or salmonella or selenium poisoning or superpotency to iron poisoning. Those were all things that we found in recalled products, all defects that are very real today.

These risk and health benefits were

identified by FDA epidemiologists.

We also felt that an important benefit would be that consumers would spend less time searching for safely manufactured products with standardization, with uniform quality standards, consumers will spend less time shopping for differences in quality based on different manufacturing practices, and if we can just save a few minutes every year for adults across the entire population of adult users, it can actually save quite a bit, and we felt that there would be fewer product recalls.

We felt the industry will incur significant compliance costs. We felt, in our analysis, that the major costs will come from recordkeeping and final product testing. Those who aren't doing final product testing now and will do final product testing to comply with the regulation will incur a fairly significant cost, and we tried to measure that.

But we also recognize that firms will incur capital improvements costs and costs for new laboratory equipment, and a whole range of provisions, but the two major costs we felt for this industry are in recordkeeping and final

product testing.

I am just going to say a word, a brief word about how we actually measured the health benefits. It is complicated, and there is quite a bit of uncertainty in our analysis, so we would welcome your comments as you read it. I can only go over the highlights, and I don't think the highlights really do justice to the real complexity of the analysis.

We had to do original research, and there isn't so much existing literature or existing data that we could use, and because we did original research, we would like your comments on it, and we would like it if you could provide data if you have any about health risks that you have identified.

We used the quality-adjusted life method, and to do that, we looked at the loss of functionality, for instance, from lead poisoning. A person who incurs lead poisoning from consuming an adulterated product, they would lose the ability to walk up stairs for the period of their illness, and they would also lose their productivity, they wouldn't be able to go to work, so we tried to measure that, and they would incur the costs of the direct medical interventions, the doctor's time and

the hospital's time, and things like that.

So, for all the illnesses that we identified as very real from contaminated products, we tried to assess what those costs would be per illness and per severity, and then we looked at the duration of the illness in days, so if a person were out for a week, we would look at that loss in productivity for the week.

As you can imagine, there isn't an existing database that you can just go to, so we had to rely heavily on our epidemiologists, and we had to use Monte Carlo simulation to help us characterize the uncertainty in our analysis.

We felt that if the industry complies with the GMPs, consumers will change their behavior. They will be able to shop less, and more precisely, they will spend less time shopping for purchase. They will spend less time searching for various products.

They will spend less time reading product labels and other literature. They will spend less time comparing one product with other products. They will spend less time searching on the Internet for different manufacturing practices. They will spend less time examining the product itself or

thinking about the product and second-guessing their final decisions.

There will just be more consumer confidence. Although that is difficult to measure because there aren't formal studies, we did rely on studies that looked at this phenomenon in other industries.

We looked at this phenomenon in the drugstore industry and grocery store industry, and other use-of-time studies. Again, because there is quite a bit of uncertainty, we used Monte Carlo simulations to help us characterize that uncertainty.

The results of our analysis for the benefits are shown in this slide. We expect that there will be $105 million worth of fewer illnesses, there will be $109 million worth of reduced consumer search, and about $3 million worth of fewer product recalls, but don't let that false precision fool you.

We recognize there is quite a bit of uncertainty in this analysis and that the benefits could be quite a bit higher, they could be quite a bit lower, these are really just the mean estimates, and that total is $217 million in total

social benefits.

We feel that this industry will incur a large compliance cost, and we estimated that to be about $86 million per year, so the benefits do exceed the cost, and by exceeding the cost, they justify the costs, we felt, but there will be a significant impact on firms that don't already comply with the proposed provisions.

So, very small firms could incur a cost of $38,000 per firm per year if they are not already complying, and we feel this is an average estimate, and small firms will incur, we feel, about $61,000 per firm per year, and the large firms will incur costs of about $47,000 per year.

The key sources of our uncertainty, these costs are caused by a change in practice, so with the adoption of new practices, firms must comply with the requirements for physical plant if they have to incur capital improvements, such as for replacing of floors and walls with smooth, hard surfaces, there will be a cost for that.

You may be required to buy equipment and instrumentation controls. You may have to adopt a quality control or laboratory operation if you don't already have one. Our survey showed that 85

percent of firms out there have a Quality Control Unit already, but that means 15 percent don't, so for those 15 percent, there will be a cost for a new QC Unit.

The key sources of our uncertainty in our cost estimate are the number and costs of tests per batch, the number and cost of tests per contaminant testing, the costs in creating new records, and the cost to investigate consumer complaints.

We have some estimate of that. We have some literature for that, and we got some information from our survey, but we are very eager to hear your comments, and if you could provide data that could help us improve our analysis, that would certainly strengthen the rule.

We recognize that the burden is going to be significant on many firms, but especially the very smallest firms, and to estimate the number of firms that are at risk of going out of business, we recognize that there may be many hundreds that are at risk of going out of business.

We looked at those firms that now have revenues of less than $500,000 per year. If they incur the average or higher compliance costs of let's say $38,000 per firm, and their revenues are

now less than $500,000 per firm, that is going to reduce their profitability fairly significantly, so they would be at risk of going out of business.

So, we did look at at least one regulatory option to help those small firms by giving them a three-year compliance period to help them meet the requirements over a longer period.

That's it for me.

DR. MUSSER: Thank you, Peter, there are a couple of questions for you.

Why is the impact greater on small firms than on large firms?

MR. VARDON: We found from the survey that large firms are more likely to be in compliance, so the types of provisions that they would have to do to meet the proposed requirements are less, more large firms are already doing final product testing than small firms.

DR. MUSSER: If the goal of the proposed rule is to protect the consumer from adulterated product, what is the FDA justification for a three-year time frame for compliance with these GMPs for the smaller manufacturers versus the one-year period for compliance in the case of larger manufacturers?