MR. VARDON: That is a very good question. We do want to protect the consumer, but we also recognize that this rule is going to have a very significant impact on many small businesses, so to reduce that impact, there is a tradeoff, and we felt this would help us achieve that tradeoff, a proper balance, but on the other hand, if those object to it, we certainly would welcome your comments.

DR. MUSSER: Another question. Did you evaluate the cost of samples of finished products on each labeling run?

MR. VARDON: We did look at the cost of holding samples as an aspect of the cost of testing.

DR. MUSSER: There is a multi-part question here. Sometimes only one small bottle is poured in a run. Can a batch sample be kept versus a sample in every bottling run?

Yes, a batch could be kept according to the way the rule is written, a batch sample rather than every individual product.

In the preamble, there are only four cases of microbial incidents cited in contrast to the very large number of cases in the food supply. Why

have you placed such a significant disproportionate burden of testing for microbial levels on small companies that process a large number of batches of products?

MS. STRAUSS: I will mention that in the preamble, the examples of manufacturing problems that we cite are just that example, it is not intended to be a comprehensive inclusive list of all of the various problems.

MR. VARDON: I should say also there is an issue of under-reporting, that the number of reported incidents probably doesn't reflect the total number of incidents.

MS. STRAUSS: So, it is kind of a combination of in the preamble where we discuss the rule, we have given examples, in the economic impact analysis, they give examples and address the under-reporting issue.

MR. VARDON: In my experience, most questions actually aren't about the economics. I am happy to turn it over to the other issues.

DR. MUSSER: There are actually some more, and you have more time, so you have to stand up there.

How many product recalls are there

currently per year and how does that compare to drug and food recall?

MR. VARDON: I don't know how it compares to drug and food, but there are about 10 or 12 recalls a year, I would say 10 Class I's and 10 Class II's, and those Class I and Class II recalls are those that are potentially health-threatening, so about 20 per year that I am aware of, and that is why preventing recalls only created a benefit of about $3 million per year, so it's a smaller benefit.

DR. MUSSER: Another multi-part question. In federal rulemaking, is there a requirement that benefits exceed cost?

MR. VARDON: That is a very good question. They do not have to exceed costs, they only have to justify the costs, so if you can find an important rationale, a persuasive rationale for a rule even when the costs exceed the benefits, then, the rule still can be promulgated, but in this case, we felt that the benefits clearly exceeded the costs.

DR. MUSSER: If we believe costs are much higher, what would be the impact of a higher cost on the ability to promulgate a rule?

MR. VARDON: It would certainly reduce it.

We didn't accept some of the other regulatory options specifically because the costs were so much higher, we couldn't find commensurate benefit.

DR. MUSSER: I don't know if this is a question or not. Industry generally supports a rule, but believes costs should be more accurately estimated.

MR. VARDON: Well, we would like that also. Our problem, as I mentioned, was that there is very little existing data, there is very little existing literature, so we had to do the best we could, but part of this comment period is an invitation for you to provide that sort of information.

If you have the health records, if you can tell us what sort of adverse events that you have experienced, that would certainly help improve our analysis, but in the absence of data, in the absence of literature, we tried to do the best we could, so we used Monte Carlo simulations and we used a variety of analyses and sensitivity analysis to characterize our uncertainty.

DR. MUSSER: Please explain how you reached your assumption of the average cost of an analytical test.

MR. VARDON: There is published literature about that, and there are independent laboratories that publish their prices for those things, but that is an area of uncertainty for us.

We recognize that there are possibly economies of scale, people who have repetitive tests, the price can fall down, or if you just do a rare, random periodic test, the costs may be very high.

If you have to create a new test, the cost can be very high. We actually did try to assess what those costs are. We met with people in the industry actually to give us their expert opinion about that, but we primarily relied on published prices.

DR. MUSSER: Along the same vein then, costs per year estimates appear low, 47,000 a year does not pay for one employee, yet, I must assemble a Quality Assurance Unit and conduct tests, do audits on supplies, and upgrade equipment.

MR. VARDON: It is only an average. In our survey, we asked people what practices they are currently following. There are about 80 provisions in this, and we had about even more questions asking are you following this practice now, are you

following that practice now, and we found that many in the industry are following many of the practices.

Like I mentioned, 85 percent of the industry already have a QC Unit, but we certainly recognize for those firms that aren't following those provisions, the costs could be considerably higher. That is only an average.

DR. MUSSER: The final question I have is what is the cost of FDA inspections.

MR. VARDON: We didn't look at that.

DR. MUSSER: Okay.

MR. VARDON: We can also open this up to try to address some of the remainder of the questions. We only have about 10 minutes left before lunch, but I think we would be happy to stay longer if you would like to address those questions.

Also, I would like to ask how many people would like to stay for the afternoon session? How many people plan to participate in the Small Business Forum? I would say about half the audience, maybe three-quarters of the audience. Okay. That will just help us in our planning.

Why don't we just get then to the next

questions and we will just stay as long as it is comfortable. How is that? Okay, let's go.

Will the method validation be product contaminant and/or ingredient specific? Is there a provision for the certification, registration of laboratories, such as FDA, ISO, et cetera?

DR. MUSSER: Method validation would be for both contaminants and ingredients. Currently, there is no provision for registration of laboratories by the FDA.

MR. VARDON: Somebody asked can we obtain a copy of the economic analysis, and another has asked will the slides be available or transcripts.

The slides and transcripts will be available and the economic analysis is actually in the proposal. It is about 150 pages, so it is available on line. I suggest getting the PDF version if you are going to download it.

The slides will be available I think in a couple of weeks--will that be correct--on our FDA web site, and transcripts will be available of this meeting and all our public meetings in the dockets.

The definitions of the proposed rule reflect that a batch should be produced according to a single manufacturing record during the same

cycle of manufacture.

Assuming a batch needs to be fully tested at release for all dietary ingredients, can a batch record be composed of several sub-batches each with its own weighing and manufacturing section, the testing of the full batch by a statistical sampling regimen?

DR. MUSSER: I am going to attempt to answer this because I think I understand what the question is asking. I believe what the test is asking is can we take subsamples of the final batch and do different testing on each part of that batch for individual components that have been specified in the master manufacturing record.

I believe that that would be acceptable according to the way the rule is written. In other words, let's say you had five components and five different tests. You could take statistical subsampling of the final batch, run five different analyses of those subsamples to confirm that it met your specifications.

MR. VARDON: The proposed rule appears to be QC or testing oriented. Steve used the term "quality assurance," which implies additional controls. He also identified, but didn't

specifically state vendor management controls.

Can a quality system with documented validated processes be used in place of testing controls?

DR. MUSSER: Maybe if I had more information, that might be possible, but I think not the way the rule is currently written.

MR. VARDON: Does the CGMP exemption for persons who handle raw agricultural commodities extend to drying and cutting operations? In other words, when does a raw agricultural commodity become less or more than raw?

MS. STRAUSS: Good question. Anything to do with harvesting, transporting, that doesn't involve the processes that we describe as manufacturing, packaging, labeling, if it is just harvesting, transporting to someone else that is going to process it, those operations would be exempt under the exemption we proposed.

MR. VARDON: If you take a validated method that has been shown to work on a product, a form of method transfer protocol to another lab in which accuracy and precision is verified, is this sufficient to meet the requirements?

DR. MUSSER: Probably not. I say that

because there really wasn't sufficient information in that question, but I think I get the gist of it, and, no, not under the current regulation.

MR. VARDON: For a method that has been validated by USP or AOAC, what parameters need to be checked for method validation in-house on one's product? Do you have to test for accuracy, precision, specificity, linearity, range?

DR. MUSSER: Yes, you would have to test all of those particular factors that are outlined in numerous documents, and I would probably refer you to the ISO-17025 guidelines for defining those. Those are really very well established guidelines now for validation of analytical methods.

MR. VARDON: We have had a number of questions about enforcement, so I will get to a few of those now.

Who will be conducting the inspections of dietary supplement facilities, will it be FDA, will it be state inspectors, and, if FDA, has Congress provided funding for additional inspections?

MS. STRAUSS: Sort of a budget issue, and inasmuch as the final rule is down the road, some of those questions are impossible to answer, in fact, most of them, but generally, the inspectors

that are currently doing the inspections in the field offices now would be doing them in the future. They would just have more inspectors to do it unless there is additional funds provided.

MR. VARDON: Will the field enforcement people be educated in the background and science related to dietary supplement ingredients? How will enforcement be handled in light of Commissioner McClellan's call for more stringent enforcement in dietary supplement manufacturers?

Will supplement manufacturers have to register with the Agency?

MS. STRAUSS: Yes, that is part of the Bioterrorism proposal, so that is yes, and I think the Agency does inspections, as many inspections as possible and given the budgetary resources. I think that is about the best answer we can give at this point.

MR. VARDON: Is it currently legal to sell a dietary supplement that doesn't meet its label claims?

MS. STRAUSS: No.

MR. VARDON: This is regarding reserve samples. The proposed rule requires now a three-year retention of representative reserve

samples for each batch of dietary ingredients or dietary supplements.

What if three years exceeds the expiration dating?

MS. STRAUSS: That's a good point, and as we have said in the proposal, what we have established as a recordkeeping requirement and why, and if there is a better time frame or a better way to express that, we would be interested in hearing what your comments are.

MR. VARDON: It is just a couple of minutes to noon. Would you like to stay longer to have more questions answered, or would you like to break for lunch? Maybe a show of hands for those who want to break. A clear majority want to continue.

How do you draw the line between adverse events reporting and CGMP-related problems?

MS. STRAUSS: We have identified that and say if an adverse event is related to product quality, it is part of CGMP. If it's related to a pharmacologically active substance that would cause an adverse event, it is not a CGMP issue.

That's the dividing line, is if it's a dietary ingredient, if it's a pharmacological

activity that causes the adverse event, it's not a GMP issue. if it's contaminated too much, too little, off color, those kinds of issues are product quality issues, those are GMP issues.

MR. VARDON: This related to a GRAS ingredient. There are a large number of excipients used in the dietary supplements that are listed in NF and in Food Chemical Codex that have been used for many years and don't meet a food additive status, nor is GRAS for its common use.

Has any thought been given to handling these in--I can't read the rest of it. Can you say a word about GRAS?

MS. STRAUSS: I can say what we propose. If it's not a dietary ingredient, it would need to be an approved food additive or GRAS, and if it's not currently GRAS, then, the manufacturer would need to do a self-GRAS, recognizing that there are some substances that are clearly not dietary ingredients, you need to handle them in some sort of way.

MR. VARDON: In your cost impact analysis, did I consider the cost of every site to revalidate validated methods? This should have a significant cost impact on the industry.

We tried to address that, but that is actually very hard, so one of the things we could ask of you is to tell us how much that would be. If you could send in your analysis, that would help us improve our analysis.

You seem to use the term "adulteration" interchangeably with identity, purity, quality, strength, and composition, when, in fact, there are many examples where adulteration is a more limited term.

To what extent do these GMPs actually require specifications to be set? Only those that relate to adulteration as defined in the FD&C Act?

MS. STRAUSS: Sara included in her remarks what we interpret as identity, purity, quality, strength, and composition. They really relate to contaminants, to the identity of a dietary ingredient, looking at what is claimed on the label to be sure that the product is not contaminated.

Those are the kinds of things that we considered when looking at what kinds of specifications would be required.

MR. VARDON: For test methods, if a test exists in USP and the lab has a separate method for that test, is the testing lab obligated to use the

USP method?

DR. MUSSER: There is an instance where a USP method might be required for I believe it is a particular vitamin. I would have to check. Just because the method is in USP, though, as the rule is proposed, it does not mean that you have to use the USP method.

In other words, let's say, for example, there is a USP method for caffeine. If you have another method that is validated and works in your laboratory to your specifications that is different from the one specified in USP, this proposed rule would allow you to use that method as an alternative to the USP method.

MR. VARDON: Do manufacturers of bovine-derived supplements have to test for BSE?

MS. STRAUSS: That is one of the questions that we have asked in the preamble, and there is considerable discussion about BSE and what testing methods are available or not available, so I would refer you to that discussion, as well as to looking at other kinds of guidance for other kind of biologics that are animal derived, and to get your comments on what kind of requirements should be proposed for those very special animal-derived

ingredients that have those special concerns for contamination.

MR. VARDON: This question is in regard to cleaning SOPs and cleaning validation. Should automated production equipment be performed in compliance with 21 CFR Part 2?

MS. STRAUSS: I don't understand the question.

MR. VARDON: Do you understand it?

DR. MUSSER: Part 11. You are talking about the electronic recordkeeping, Part 11 is electronic recordkeeping.

MS. STRAUSS: Yes, if you have electronic records, they would need to comply.

MR. VARDON: If you test every lot of raw materials received and used in a particular batch, do you still have to check for each ingredient in the finished product? We can then choose a marker of compounds, such as for water-soluble vitamins and fat-soluble vitamins.

MS. STRAUSS: They are saying if you test every incoming, would you need to test the finished product?

DR. MUSSER: Yes.

MS. STRAUSS: Yes, if you test each

incoming and you can confirm in the master manufacturing record that it is not contaminated, nothing has happened to it, then, you would not need to retest the final product because as we have those flexible testing requirements, it is either the finished product or the incoming and in-process.

MR. VARDON: This is regarding the EPA water requirements also. Please define the requirements or Agency expectations to ensure water meets the EPA requirements. If the water is potable and you have data of compliance to EPA requirements, I guess it's publicly available water sufficient.

MS. STRAUSS: In the preamble, as I mentioned earlier, the water requirements really want to be sure that any well water that is not a municipal source meets EPA drinking water regulations, and if municipal water is used and you have results of those testing from a municipality that ensures that it does meet the standards, that is sufficient, and we talk about that in the preamble.

MR. VARDON: Is private well water or ground water acceptable?

MS. STRAUSS: It would need to be tested to ensure it meets the drinking water standards.

MR. VARDON: Will cleaning validation be required?

MS. STRAUSS: We haven't required any process validation.

MR. VARDON: Is a product that possesses the identity, purity, strength, and composition that it purports to possess, but that was not manufactured according to CGMP is proposed adulterated?

MS. STRAUSS: If it is not manufactured in accordance with the final rule for dietary supplements, it would be adulterated. Section 402(g) says that if there is a CGMP rule for dietary supplements, and it is not met, then, it is adulterated.

MR. VARDON: Why don't dietary supplement GMPs require a tamper-resistant packaging?

MS. STRAUSS: If you think it should, tell us.

MR. VARDON: If there is a USP monograph for a dietary supplement, must the dietary supplement meet the monograph?

DR. MUSSER: No. We clearly state in the

Method that it has to meet your specifications, not those of another party.

MR. VARDON: Is the food code a requirement or only guidance?

MS. STRAUSS: The food code? It's confusing parts in it. The CGMP for food is required, the food code is another document, and I am not sure about that.

MR. VARDON: Steve said no skip lot program is allowed for incoming ingredients, yet, this is allowed for drug GMPs. We have gotten a number of questions about this, so maybe Steve could address that, and why is the standard higher for supplements than drugs?

MS. STRAUSS: If you look at 211, and I looked because this is a question that came up before, the CGMP for finished pharmaceutical products does not address skip lot testing. It is not permissible, it is not included in their CGMP, so I don't know.

DR. MUSSER: That was my understanding.

MR. VARDON: If one is using fresh botanical material for processing into a hydro-alcoholic--I don't know what this word is--

DR. MUSSER: Tincture.

MR. VARDON: Tincture--how is one supposed to test when immediate processing is necessary?

DR. MUSSER: I guess if the final product is the tincture, then, you could test the final product for whatever specifications were included. If the tincture were included as another ingredient, then, you could test the ingredient that the tincture met the specifications that you required. I hope that answered that question.

MR. VARDON: This questioner states in one case you say you can validate a supplier, rely on the C of A, and then in another case, you say no skip lot testing.

Can a supplier be validated if the C of A is shown to be reliable and use one I.D. test, in other words, will that serve as an appropriate I.D. test?

MS. STRAUSS: This is really a question that keeps coming back, and if you read the preamble, and you understand the purpose of the rule, the purpose of the rule is to prevent adulteration, to make sure that the label on a dietary supplement includes what it says, in the amount it says, and it is not contaminated.

In order to do that, you have to have some

testing, and it has to be tested somewhere along the way, either finished product or incoming and in-process.

We have discussed Certificates of Analysis in the preamble. We have not included them as appropriate in the codified proposal. We have said in the Laboratory Operations portion, in our preamble, that while there are laboratory requirements, they can be off site or on site.

So, if you look at the testing requirements and fulfill the testing requirements, we don't really say who has to do them, we say what needs to be done. So, if you have a supplier that tests for everything that you have specified, every time, just as you would send that to an outside lab if it came in to you, that would meet what we propose.

We have not proposed a Certificate of Analysis, we have proposed testing. So, a validated Certificate of Analysis that involves skip lot testing, if you are relying on it for your label, and you are not doing final product testing, that would not be appropriate.

If you have an outside lab doing it, or, say, you are not doing final product testing, and

you have an outside lab testing your incoming, that would be appropriate, but they would need to test every shipment lot for the specifications that you have included for that particular component.

The outcome we are looking for is that a label accurately describes what is in the product and it is not contaminated. If we were to rely on Certificates of Analysis to confirm what is in that product, we would be not having reliable evidence that the testing was performed.

I don't know how much more clear or what words to make that clear, but a Certificate of Analysis that is validated, that is reliable because you have visited them periodically is not what we have intended in this proposal.

MR. VARDON: This questioner asks are we suggesting that a manufacturer may choose whether to test incoming materials rather than finished products.

MS. STRAUSS: Yes. We have proposed the flexibility for two reasons, one for economic reasons, the other for scientific methods reasons. If you have a finished product that has four ingredients, for example, and you can test at the finished product stage for three, but not for four.

You can test for the three at the finished product stage and test for the one at incoming and in-process, so it is not all or none, you can decide.

MR. VARDON: In the absence of stability testing and expiration dating requirements, how can the consumer be assured that products meet DSHEA requirements, such as 100 percent of label claims throughout shelf life? In other words, why didn't we include stability testing?

MS. STRAUSS: This is a question we have answered before. Logically, if you have an expiration date, it should be based on an active ingredient, and because the active ingredients are unknown, it would be inappropriate to have proposed at this particular time, because the actives aren't known for botanicals, for example, an expiration date. An expiration date would not necessarily be meaningful to a consumer if it wasn't based on the active ingredients.

As I mentioned before, we have also asked for comment on whether there should be expiration dates for certain dietary ingredients, certain dietary supplements, and not for others, for example, vitamins, but not for botanicals.

MR. VARDON: Related to that, have we considered fewer requirements for companies working with whole form botanicals?

No, we didn't actually look at that as a regulatory option, but that may be worth looking at, so if you could provide information about why the risks or the sort of controls made, fewer controls might be still reliable, so achieve the same results for this option, that would be very helpful to us.

When testing requirements where current and generally available technology exists, does that mean that if a compendial standard exists, it should be used?

DR. MUSSER: The compendial standard, whenever, this is speaking from personal experience now, if something were available that I could start with, that would certainly be the easiest point to start with, but it doesn't mean, the rule does not mean that you have to start with that.

If you feel that you want to come up with your own completely new method, then, the rule certainly allows you to do so. You are not required to use the compendial standard.

MR. VARDON: If one manufacturer develops

a new method or technology for a test, are all manufacturers then subject to testing requirements?

DR. MUSSER: No, this is per manufacturer.

MR. VARDON: Aren't tamper-resistant and child-resistant systems overseen by the Consumer Product Safety Commission, and not FDA?

MS. STRAUSS: Yes.

MR. VARDON: We have already addressed water quality standards. If I am skipping questions, it might be because I can't read your handwriting. It is not because I am trying to avoid questions.

What documentation is required--I think we addressed that--regarding EPA drinking water requirements.

In lieu of doing extensive end product testing, why doesn't the current proposal allow for the use of statistical process control and process capabilities testing? This is allowed for drugs and is also found in the USP.

MS. STRAUSS: The drug CGMP doesn't allow statistical sampling. If you look at 211, for incoming, it requires at least one identity test and a reliable Certificate of Analysis, and it also requires final product testing. It doesn't talk

about skip lot testing and good manufacturing practices.

What is there by regulation and what is common practice may not be the same, I don't know, but I know what, you know, because this question has come up several times, I have gone back and looked at what is required for drugs, and 21 CFR 211 doesn't say anywhere anything about skip lot testing or statistical analysis or testing of final product or incoming.

MR. VARDON: The terms "design" and "ensure adequate" implies some type of process has occurred. Does this process have to be documented and is the documentation subject to review by FDA? In other words, is documentation required to ensure adequate design?

MS. STRAUSS: Of equipment?

MR. VARDON: Yes.

MS. STRAUSS: The only records we have proposed to require are calibration records, consumer complaint records, master batch records, and master manufacturing records, and batch production records. We haven't required any records on design of equipment, just those records that I mentioned.

MR. VARDON: Do requirements for sanitizing require verification of a 5-log reduction in microorganisms under every specific application, or can a general certification of effectiveness from the manufacturer of the sanitizing agent suffice?

MS. STRAUSS: As we proposed it, there would need to be confirmation that the product used achieved that 5-log reduction.

MR. VARDON: Why are ingredients, particularly excipients, that are currently used in drugs, HPMC, for example, not allowed in supplements without further action, such as a 75-day notice?

MS. STRAUSS: They are not. A 75-day notice is for a new dietary ingredient, which is not an excipient. An excipient is something different. If there is an excipient used in drugs, I believe that they are GRAS.

MR. VARDON: Does the proposal require that master manufacturing records include corrective action plans for use when the specification is not met? Can you clarify that?

MS. STRAUSS: A corrective action plan, if it something that is likely to occur frequently,

such that you can in advance plan for it, a corrective action plan would be required.

MR. VARDON: This is a more general question. What is FDA's rationale for proposing two kinds of consumer complaints, those based on GMPs and those based on ingredient safety issues?

MS. STRAUSS: If you think that we should not have done that, give us a comment that tells us that. Our rationale was we could see that there is some consumer complaints that are really related more to the dietary ingredient, and not how the product is manufactured.

If you think that we should expand that definition that we have used in our CGMP, you know, tell us that and tell us why.

MR. VARDON: Does FDA envision a provision for allowing companies who demonstrate a comprehensive systems-based approach to quality assurance including process validation to employ a parametric-based release principle, such as tracer testing, composite testing, and skip lot testing as allowed by USP?

So, are there going to be exemptions, I guess, for comprehensive systems?

MS. STRAUSS: No. The GMP would need to

be followed as proposed.

MR. VARDON: The proposal requires that you maintain clean and sanitized, as necessary, equipment, contact services, utensils.

Is it correct to interpret sanitation is not necessary if justification can be provided, such as for dry products manufactured that are not susceptible to microbial growth and products that have low water activity?

In addition, would it be acceptable not to perform sanitation if supported by cleaning validation and microbial monitoring?

MS. STRAUSS: That's a long question.

MR. VARDON: Would you like me to repeat it?

MS. STRAUSS: Yes.

MR. VARDON: The proposal requires that you maintain clean and sanitized, as necessary, equipment.

MS. STRAUSS: We need to stop there. That is what we have proposed. If you look also, there are some requirements that relate to both wet and dry kinds of use of equipment. I don't have them all, you know, right in my memory, memorized, but there are different requirements for those two

different kinds of situations.

When we say the phrase "as necessary," the manufacturer may have discretion there and should have, you know, good reasons for why they have done what they have done.

MR. VARDON: Okay. I will go on.

The proposal requires specifications to guard against adulteration. It then specifies the need for specs for identity, purity, quality, strength, and composition.

How do these two requirements mesh, is it FDA's intent to require under this regulation specifications and tests for quality attributes that do not directly relate to adulteration, such as disintegration, hardness tests, and to assay for a claimed ingredient? How about particle size, moisture content, and bulk density for powdered ingredients?

DR. MUSSER: I am going to have to read this, so I can go through all of this. We have defined identity, purity, quality, strength, and composition, and how that relates to adulteration in the preamble.

That will answer your first question on how these particular items mesh.

The next part of your question, is it FDA's intent to require under the regulation specifications and tests for quality attributes that do not directly relate to adulteration, such as disintegration, hardness tests, and assay for claimed ingredients?

If you claim an ingredient is there, then, you have to test for it, but it would not require--the rule as it is currently written would not require disintegration and hardness tests, nor would it require particle size, moisture content, and bulk density unless you have specified that as part of your manufacturing record.

So, if you specify it, you have to meet it.

MR. VARDON: Is the manufacturer of either the dietary ingredient or finished dietary supplement responsible for ensuring component manufacturers are in compliance?

Is the manufacturer of either the dietary ingredient or finished dietary supplement responsible for ensuring component manufacturers are in compliance with the rule?

MS. STRAUSS: No. They will set up their specifications and then test in accordance with

them.

MR. VARDON: The proposal allows for reliance on ingredient manufacturers' Certificate of Analysis as long as at least one I.D. test is conducted and the manufacturer is established. That is a statement.

MS. STRAUSS: That's an incorrect statement.

MR. VARDON: And that is an incorrect statement.

In the proposed rule, we must test each lot of ingredients, and in the preamble, we are told that reliance on supplier certificate is not appropriate. Why are supplements being held to this much higher standard?

MS. STRAUSS: The reason they don't use Certificates of Analysis is because they do not ensure--if you are relying on testing to confirm the label, the Certificate of Analysis is not sufficient. We have evidence that shows that it is not sufficient.

We have not proposed a Certificate of Analysis be appropriate, and if you go back and look at the, for example, the industry outline that was submitted to us, a Certificate of Analysis is

included in that outline providing it is reliable and when identity test is done.

Final product testing also appears to be suggested, but because we have provided that flexibility of when you can test, you can't rely on a Certificate of Analysis in place of testing. I mean that is just how we proposed it.

If you think there is some other way, if you think that we should be proposing something else, less flexible, tell us. All I can tell you is what we have proposed.

MR. VARDON: We just have a couple of questions left.

Isn't the testing requirement for each batch of finished product much more stringent than food GMPs? If a requirement for a product is that it meets FCC guidelines for that product, that could include microtoxins or aflatoxins, that lack antibiotic activity.

Most tests like these would not be completed for every batch of a food product, and some of these specifications could be invalid for a product by the way it is manufactured.

MS. STRAUSS: That is a long question. There are differences in the characteristics of

dietary ingredients, dietary supplements, and foods. My green pea, green bean example holds. I mean to test the final product for identity.

For microbes, I am not sure what the manufacturers actually do or what is actually required in the food GMP. We look at dietary ingredients based on them as a unique characteristic. Most of the CGMPs in foods are based on sanitation.

MR. VARDON: One last question. What if the manufacturer sets their specs, tests, finds the final product within the specs, and the manufacturer is within the CGMP in other areas, but an independent lab test doesn't know the manufacturer's specs and fails the product.

The manufacturer retests, finds the product still within specs. Does this differ from the situation as it now exists, and do these independent lab tests form an adequate basis for establishing compliance with the GMPs?

DR. MUSSER: It is a difficult question. I don't know the independent laboratory would test for something which they didn't know what they were looking for.

I will give you an example. If you set a

specification of 10 milligrams of caffeine per tab, and you find that you have 10 milligrams in that tablet, and it is on the label.

A third party tests and finds that you have 5 milligrams on the tablet. I don't know how they fail your product. You have validated the test, you have confirmed that your product meets the specifications on the label. So, I don't know how the third party fits into this because they wouldn't really be in a position to fail your product.

I mean I can't imagine the case where that would happen and how that would relate to our regulatory authority.

MR. VARDON: It is 12:30 now. Let's meet back here at 1:30.

[Whereupon, at 12:30 p.m., the proceedings were recessed, to be resumed at 1:30 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:35 p.m.]

MR. VARDON: Because we do have a long program, why don't we get started.

Our first speaker this afternoon is Richard Williams. Richard Williams has been with the Agency for 22 years, so he might be our most senior representative today. Richard has a degree in business management, and he served in the U.S. Army during Vietnam, he is a Vietnam vet, after which he went to Virginia Tech to get his Ph.D. in economics, after which he taught for a couple of years at Virginia Tech and then he went to Washington and Lee University.

From there, he joined the FDA in 1980. He is currently the director of the Division of Market Studies and as the division director, he is responsible for the economic analysis and for the statisticians, epidemiologists, physicians, psychologists, sociologists, nutritionists, and other disciplines. It is a complicated division.

Through his many years here at FDA, Richard has analyzed such diverse issues as the costs and benefits of banning lead acetate, delisting colors in sulfites, revising the food

standards, the control of Salmonella enteritidis in shell eggs.

Richard was very involved in the Nutrition Labeling and Education Act. Richard has been involved in the HACCP for seafood processors and juice, and Richard has negotiated the U.S. position on various matters under the U.S. and Canada Free Trade Act, so he really is a well-experienced person. He is also an expert in risk analysis particularly risk management, and has recently published papers on risk tradeoffs.

In addition, Dr. Williams is currently responsible for developing a series of courses in risk analysis for the Food Risk Management Group. Richard is an expert on small business law and guidance, and that is what he is going to talk on today.

Richard.

Regulatory Flexibility Act and How to Comment

DR. WILLIAMS: Good afternoon. Thank you, Peter, for the kind introduction. I don't know about including the Vietnam experience, but I will go with it.

The point of this part of the session really goes to our outreach efforts for small

businesses. I know there are a number of you here that are not representing small businesses, but that really is the point of this short session.

The reason that we do this is because we understand that small business people generally do not have teams of regulatory staff who pour over regulations, legal counsel, and so forth, and really understand how to work the process, if you will.

I think Karen may have mentioned it briefly, but for those of you who are sort of new to the regulatory process, just let me make sure that you know where we are at. We did have an Advance Notice of Proposed Rulemaking. That is where we just go out and ask questions what should we do.

We do have a proposal on the street now. By now, I assume all of you have at least seen it, if not poured through every word on it. We are now in the process of getting comments, and this is the point at which anybody who is going to be affected by this regulation, or anybody at all for that matter, can actually make an impact on what the final regulation will look like, because that is what is key.

If you are here to find out what you have to do today, you are premature. Today is the day to find out what we have proposed, to get ideas for suggestions to make to us about how you would like us to change what it is we have proposed, and you will not be required to do anything until we evaluate what your comments are and we must, by law, evaluate all of your comments.

We come to some final decisions and then those decisions will be put into a final rule, and at some point after that final rule, there will be a compliance date by which time you have to comply.

So, the point of this part is to tell you how you can actually make comments that will affect what we do.

We would have this anyway, I hope, but we are required by law to do a lot of special things for small businesses. The law really started with the Regulatory Flexibility Act of 1980. That Act only required us to do analyses basically and it required FDA to look at those analyses, but it really didn't have a lot of teeth, and it really didn't make I don't think a tremendous difference to small businesses.

In 1996, there was an amendment to the

Regulatory Flexibility Act known as SBREFA, Small Business Regulatory Enforcement and Fairness Act, and that amendment really did put a lot of teeth in the ability of small firms to effect regulation.

It required a lot of very specific things for the economists to analyze. It also required specifically that agencies reach out to small businesses, explain what it is they are trying to do, and solicit comments from them, and this meeting is simply a part of that. We had been doing this even prior to the proposal, talking to small businesses, but we are doing it now, and we are really trying to get what your input is.

The law allows more influences over the development of regulations. We must by law list a number of regulatory options. We have to consider how to provide relief to small businesses from parts of regulations that might seem overly burdensome.

It doesn't require us to make any specific decisions, it just says we must analyze what those options are and we also must consider whether or not we can achieve our objectives and grant small businesses some sort of relief, and our decisions are judicially reviewable, as well.

There is additional compliance assistance for federal rules. One of the things that I think is most important is that when we do have a final rule, we are also required to write a guidance for small business, written in plain English, stating exactly what it is that you have to do, and that is something you should look for. Hopefully, it will be out right around the same time as the final rule, and I think it makes it a lot easier to comply.

There are new mechanisms for addressing enforcement actions by agencies. I really don't want to get into those. There are things such as relief from civil penalties.

Suggested areas for comment. First, is the need for the rule. In the preamble to the regulation, it is really divided up into two main parts. There is one part that gives our legal justification and a scientific overview of the rule, and the other part is the economic analysis. That again is divided up into two parts.

It is divided up into a cost-benefit analysis and that is generally overseen by the Office of Management and Budget, and yet a separate section is the regulatory and flexibility analysis,

and that is the part of the analysis that addresses small businesses.

Both in the cost-benefit analysis and in the regulatory flexibility analysis, FDA describes why we think there is a need for this rule. You can comment on that.

I think one of the key things that we often get from businesses that really do seem to make an impact is what it will cost you to comply with the rule. I want to stop right here and make sure that you understand what I mean by what does it cost you to comply.

If there is something that you are already doing, you plan to continue doing it for the rest of the life of your business, and it happens to be required in this rule, that is not a cost of this rule making you continue to comply with what you are already doing.

What a cost of this rule is, is if there is something that you are not doing for whatever reason you are not doing it, and the rule says following passage of this final rule, and the implementation date, you must start doing it, that will be a new cost for you, and that is the kind of thing that we have tried to analyze by looking at

your industry, and perhaps we have gotten it right and perhaps we haven't.

What we need to hear from you is particularly where have we not got it right, what parts of it have we not got right. We obviously have listed some goals that we hope to accomplish in this rule, and primarily it is by making safer dietary supplements.

You can look at aspects of this rule and say will these aspects help us to accomplish the goal, and specifically, if you have other ideas--we do not have all of the ideas in the world on how to make safer dietary supplements--if you have other ideas on how we can make provisions to accomplish the goal of making safer dietary supplements, we do want to hear them.

I think we might have listed this twice. Do not report sensitive information. All information that comes to us through comments, and by that I mean the written comments that hopefully you all will provide, is subject to the Freedom of Information Act, it is available to the public, so I am going to be sort of speaking out of both sides of my mouth.

I am asking you to report numbers, I will

be asking you to report numbers, but I don't want you to report anything that you would be uncomfortable sharing with the world. So, this is a decision that you will have to make.

One type of information that might be interesting is what will be the impact on your profit. This is not an interesting question for cost-benefit analysis, but under the Regulatory Flexibility Act, it is a very important question, it is something that agencies are supposed to consider.

However you wish to report it, if you do wish to report it, you might say my profit will go from 10 percent to zero, or negative, or whatever. Any way that you can report it in a way that is okay to be released is fine. Again, this is what would your profit would be if the proposal were as it stands right now to become final, okay, what would happen to your profit picture.

That is something that is of interest to the government and has the potential to affect what it is we do.

Again, I will just repeat it, do not report sensitive information.

In the cost analysis, one of the main

types of costs, I guess the main type of cost that we are concerned about particularly with respect to small businesses are so-called fixed costs. Those are costs like buying a piece of equipment. You would buy the same piece of equipment, for example, if you had a very large line with lots producing 10 million products per year or a very small line only producing 10,000 products per year.

The reason that fixed costs are important is because you have a smaller sales base over which you have to pay for that piece of equipment. So, fixed costs are going to be one of the things that we are most interested in.

Kinds of things that you will know specifically about your firm or perhaps you know about your industry or some subset of your industry, changes in the number of workers. If you have to hire additional workers as a result of these new requirements, that would be something we would be interested in.

Changes in the hours worked. This is important. Here is an interesting cost that most people who are not economists--and I think probably there is only a couple of us in the room that can raise their hand to that question, are you an

economist--will know.

I have had a number of conversations even with very, very large business people, and I have talked to them about the economic concept of costs, and I said, well, how many hours of manager time will your managers have to spend in complying with this rule, whether it is learning about it, training people, making decisions, whatever, and they will sort of give me an estimate, you know, maybe it will be 10 hours per week, and they will say, yeah, but that is not a cost because we will have those managers anyway.

Well, to an economist, that is a cost because that 10 hours per week that that manager will spend in complying with the regulation doing whatever, it is 10 hours that manager will not be spending doing something else.

So, whatever those new additional activities are, that is something we are interested in, and make sure that you think about it that way.

It is new activities, things that you were not doing before, so whether it is hiring new people or taking the same people whether they are employees or managers and if they are now doing something different, both of those are considered

costs and both of those things we are interested in, and they have the ability to affect the analysis.

What kind of person will be doing something different? This matters primarily because these people are paid differently. The value of their time is different, and we do try to take that into account.

An example. Recordkeeping requirements, there are a number of recordkeeping requirements in the proposed rule, things that you might wish to comment on - what is the cost to develop and store those records. You have to train your employees to manage those records. If you do, what is the cost, how many employees are you going to train, how much does it cost per employee to train them.

You have employee turnover, so that you have to train a bunch of employees this year and the next year you might have to train a bunch more. Is your production process slowed up, is there an increased cost to production? You may also wish to comment on the benefits of the rule.

Perhaps if you have better control over your process, you will have fewer recalls, and that would be considered to be a benefit of the rule.

A more specific example, master manufacturing record. What is important here is we are looking for the frequency of these costs. For example, if it's a one time cost, that is something when the rule comes out you have to comply with it, perhaps you have to invent your master manufacturing records, you have to develop these records that one time, you don't ever foresee having to invent them again, that is a one-time cost.

Say what that is, say what that cost is, and also that's a one-time cost, and you can look in the economic analysis, you can see our estimates, and you can say, well, that's not right for me, and you might want to comment on that.

In some cases, the training costs, perhaps again you may have to train people every year. Give us the cost of training per person, give us the number of people you have to train and say I have to train people every year or every two years.

Then, finally, you might wish to comment on something like the reporting costs which might happen batch by batch. If you tell us that your costs are by batch, we want to know how many batches in a week or in a month, however you would

like to report it. Eventually, we have to get to annually because that is generally the way we report all of our costs.

This is kind of the formula we use. You don't have to multiply anything, you don't have a memorize any formula, we just put this up here. All we want are the elements of this if you care to report them, what are the number of worker affected, what is the approximate wage including the overhead for those workers.

How many additional hours of work will it take to fulfill a certain function, and then finally, what is the frequency. Those are the kinds of things that we wish to report.

Now, I said earlier don't report sensitive information. Again, if this is sensitive, don't report it, but if it is, this is the kind of information that will change the economic analysis, which will change the regulatory flexibility analysis, which the Agency must by law consider.

When we go to look at each individual requirement that we are requiring, this is the kind of information that can actually make an impact on the regulation.

Another example I think you spent a

considerable amount of time on, I understand, I was not here this morning, but a considerable amount of time spent talking about, testing costs. We do have an estimate of what the testing costs are. You can read about it, tell us if we are right, tell us if we are wrong.

Those include the identity tests, microbial tests, and tests for other contaminants, lead, aflatoxin, pesticides, et cetera, there are a number of different kinds of tests.

What kinds of things might you want to comment on? Number of tests per finished batch. If you have a finished batch, do you have a test right now that will test for everything that is in this batch that you need to test for, is there one test that covers everything.

If not, you have to do multiple tests, is it one test or multiple tests. We don't know. It is your product, it is your matrix, you know how many tests you have to do. We would like to know, how many tests do you think this will take per batch.

What will it cost you to do those tests, it will cost you to prepare samples, it will cost you to take the actual samples, it will cost you to

record them. It may cost you extra to provide the space for those samples. You may have to buy new equipment to take those samples or perhaps you are going to contract them out, and that may cost you lost production.

Those are the kinds of things, very specific things. If you can tell us, we would like to know. It will help us alter the regulatory flexibility analysis.

I think this is the last slide. Do's and don'ts. Do send specific numbers if possible. Again, if it's sensitive, don't send it. As Peter has mentioned, I have worked on a number of regulations in my regulatory career. I have looked at more comments than I care to remember, and I have looked at some pretty funny ones actually, and I have looked at some pretty good ones.

The good ones are the ones where people came in and said this is what either this regulation or this specific part of the regulation is going to cost me, this is what I am making now. There is no way I am going to make it, I am going out of business, and this is why exactly.

Or you guys got this entirely wrong, this is what you said the cost was, this is what the

cost really is, and if we have overestimated the cost and underestimated the benefits, then, perhaps we have got to reconsider. Specific numbers are extremely helpful.

I myself like the humorous ones. I have seen a number of those. We had one when we went to ban saccharin where somebody wrote in and said that they wanted to thank us for banning saccharin because then we quit killing all those rats, and they signed it, "The rats of America." So, we like the humor, too, if you want to send us that.

Most people do, actually, what we get a lot of the times is we get a lot of unsupported opinions, "I hate this rule, and I hate you." Thank you for that comment. You know, it will go in that stack, and we appreciate, you know, you taking the time out to write your comment, but it really won't make a lot of difference. What do you do with that comment, you know. You know, we are not always that popular.

Do send the comments in on time. There is a very specific timeline, and if it hasn't been covered already--

MR. VARDON: And the comments are due June 11th.

DR. WILLIAMS: June 11th. Do send your comments in by June 11th. I think they have to be postmarked by then, is that correct?

MR. VARDON: I don't know.

DR. WILLIAMS: Karen, do you know?

MS. STRAUSS: I doubt if it would be that very specific.

DR. WILLIAMS: At least get them off by June 11th, and then they will continue to flow in. It is important to us. When the comment period closes, that's it. Don't send your comments to, for example, Peter Vardon, not that he wouldn't love to hear from you, he would, but it is much easier for us if you send it to the address that is in the rule, in the document.

That is very helpful because they have to go there anyway, they have to be logged in, and then they are collated and analyzed, and eventually, Peter will read them, Karen will read them, and most likely all of us.

This is helpful just to the economists. If it is possible, I mentioned sending in specific numbers if it is possible, if you have an organization that can do surveys or anything like that, I am not suggesting that you should, but

sometimes it is nice for us to receive that kind of information if it is possible.

I am certainly not encouraging you to do that, but sometimes I think that is very helpful to send in costs of multiple firms.

Finally, I guess for the fourth maybe and last time, don't send us sensitive information.

That's it. We do welcome your comments. Please send in written comments if you can, and please make them as specific as possible.

Do we do questions now or later?

MR. VARDON: No, after Marie.

DR. WILLIAMS: Okay. It is my honor to introduce Marie Falcone, who is our Regional Small Business Representative for the Central Region of FDA. She was an FDA investigator, and she has performed domestic and foreign inspections.

She is a supervisor and she has turned her training and experience to the consultive side of FDA, and she is assisting regulated companies, such as yourself, and she has a B.A. from the University of Connecticut, is that correct?

MS. FALCONE: That's right.

DR. WILLIAMS: Welcome, Marie.

MS. FALCONE: Good afternoon, everyone. I

am very pleased to be here. I am Marie Falcone, Small Business Representative for FDA Central Region.

What I would like to do today is to put the small business representative and what we do in a context for you, so you can see how you can use us to reduce your workload. It is a free service that FDA provides to regulated industry, and if you are in my region, I am your small business representative, and you will see what that region is.

This is a list of things that we do. We do assist FDA regulated businesses by explaining laws and regulations and helping regulated industry find the guidance or the information, the registration form, the person that they need to smooth the pathway to market.

We can cut your costs of looking for things sometimes by weeks. We provide technical assistance and guidance. We act as liaison to the right person for the question when that is necessary.

We are in the field, as opposed to where we are now in headquarters, in the field outside of headquarters, and small business representatives

handle a variety of inquiries, dietary supplements, the whole range of commodities that FDA regulates as opposed to the Center staff, which are very knowledgeable and have deep knowledge in specific areas.

Our customers, small businesses, entrepreneurs, start-ups, consultants, industry associations. We don't turn away large corporations, sometimes they do call us.

We handle inquiries, we give training, we organize workshops. In some regions, there is a free service called the non-regulatory on-site inspection. You can request a small business representative to come out to your company and do an inspection, and this may become more relevant to you if and when the GMPs actually become final.

The inspections are a courtesy, they are at your request, they are confidential, and they are limited by the resources and schedule of the small business representative.

The FDA has published a variety of guidances to help you to understand the Agency, to see the things that you need to do to save time for you, and one of them is the Small Business Guide to FDA. In it are things like how to use the Federal

Register, which we learned a lot about today, how to comment on proposed regulations, how to obtain Agency documents.

Those in the business of dealing with FDA must know that. In the document world, there are requirements and there is guidance. That is a very important distinction to make. Requirements, such as law and regulation, must be followed. Guidance are FDA's best advice on how to meet those requirements, so we can help you locate those guidances and who to contact for assistance in the guide and what to do when.

By the way, I believe it has already been mentioned, but all these presentations will be on the CFSAN web site, so web addresses, phone numbers, and faxes, and so on, that we will get to later, will all be on the web site.

Keeping informed. Reviewing the biannual unified agenda. Twice a year the Federal Government puts out in the Federal Register a list of all the regulations they are planning to write or in the process of writing, and you can get that.

There is a web link to the most recent one, or, excuse me, where it is from the web site, the FDA web site that you can find it, and you can

look at that, and you can see if there is anything coming up that may affect you. That is a very good way to keep informed.

You can subscribe to the FDA's Dietary Supplement Through Labeling electronic newsletter, which is free, and you will automatically get e-mailed to you, and I subscribe to a lot of lists from the various Centers in FDA, and you will get sent to you automatically when something comes out, and you can just read it, delete it, keep it, and that way you can keep up to date, and it is absolutely free once you are on the list.

You can visit FDA's Dietary Supplement web site, and that is where all these meetings are located, the meeting in Oakland that is coming up, the May 9th satellite broadcast, which is about the same topic which will be available nationwide, and the FDA small business representative is actually posted on the site. There are at least 15 on the FDA web site where you can go and view the program, or if you have a dish, you can actually downlink your own program for free.

Now, what are the limitations? I don't set policy and I am not a regulator anymore. I cannot intervene when there is a current

investigation, there are violative conditions that warrant regulatory action.

I would like to say that I am like a vitamin pill, it is important to take me before there is a problem, not after, solving problems.

There is an inspection issue, see the District Office contact information on the Notice of Inspection. When you get inspected, along with the Notice of Inspection that FDA gives you at the beginning of each inspection, is a document like this, and it has all the district offices listed and the phone numbers.

If you have a problem with the inspection and you want to contact the district, you can see exactly how to do it or you can go to the ORA field directory. ORA stands for Office of Regulatory Affairs, and it is all the inspection people, they are all in the ORA, in the field staff.

You can go there and you can find the district office nearest to you with the district director and all the people, their phone numbers, so you can contact them, or you can go to FDA or Center for Food Safety Ombudsman, or you can go to the Small Business Administration Ombudsman, and that type of information is on the document given

to you at the beginning of the inspection, so that you have it and you can use it if you need it.

How to find your regional small business representative. If you are in Central Region, I am your representative. Northeast, Pacific, Southwest, and Southeast, we have five regions in FDA.

There is somebody here from the Pacific Region, Janet McDonald, who is a public affairs specialist out of San Francisco, and she is very knowledgeable in the food area. I knew Janet 10 years ago when she made presentations, and I was absolutely impressed at her depth of knowledge.

We not only have small business representatives, we have public affairs specialists in every district who do a lot of the same work, but they also deal with the media, so there is help out there for you. There are people who can help you and get you set in the right direction at minimal pain.

Here are the states that belong to the Pacific Region. Marcia Madrigal is the small business representative, her address, fax, e-mail. You can write us e-mail. Many of my inquiries come in through e-mail, and that makes it real easy just

to cut and paste and send back a response.

Here, I have just listed the contact information for each region, and like I said, these will all be on the FDA CFSAN web site, so don't worry about it if you can't get every single bit of information off the slides.

Southeast Region and Northeast. Marilyn Corretto, she is new, she just came into her job about a month ago. She is already saying she is overwhelmed, too.

More help in the FDA. The FDA Center for Food Safety and Applied Nutrition has an industry activity staff and that is their telephone number and e-mail. They are an excellent contact for information or just find the right person to handle your inquiry.

A very common comment to us, when somebody calls me up or they send me an e-mail, I have been to the FDA web site, I don't know where to go, I don't know what to look for, I don't know when to quit looking. We can do things like tell you exactly what you need, bing, bing, bing, here it is, and then on you go instead of weeks of wondering.

You can go to www.fda.gov and over on the

right it says Information For, and it will say consumers, industry, like that. Click on Industry and it takes you to the FDA industry web page and on that web page you can see small business representatives or the industry assistance officers at the very center, so it is not hard to find us.

All the contact information is on the web site.

MR. VARDON: Thank you, Marie.

Now, we can open it up for questions and answers about specific small business impact although we only have a couple of questions. I wonder if using cards has maybe inhibited people. Would anybody just like to ask your question on the microphone? If you would, please do so, otherwise, I will answer the questions I have in front of me, but there aren't many.

Are non-regulatory inspections available to overseas manufacturers?

MS. FALCONE: No.

MR. VARDON: This regards recordkeeping. If you never had a recall, then, fewer recalls isn't a benefit to you. This probably means you have been doing things right all along, and this means the entire rule is just a new overhead for

your business, that your business may not afford.

DR. WILLIAMS: If you have never had a recall, it may or may not mean that you are doing everything right all along. People only have recalls when, in fact, something has gone wrong with their product is actually traced back to them.

So, that is not necessarily so, but certainly if there are requirements in this rule that you are not doing now, we would like to know what those are, we would like to know what they cost you, and if you have other ideas or you have ideas about whether they are necessary or not, we would like to know that, as well.

MR. VARDON: What does judicial review mean?

DR. WILLIAMS: Within the Regulatory Flexibility Act, as amended by SBREFA, the Small Business Regulatory Enforcement and Fairness Act, parts of our analysis are actually judicial or reviewable, so, for example, in the worst of all worlds, which will never happen as long as I am here, if we didn't do an analysis, that would mean that the rule would be stayed, and there are other specific parts of the analysis that can be challenged judicially, such as whether or not we

have explained adequately why we did not adopt relief for small businesses, that sort of thing.

I don't want to get too much into that because I am not a lawyer, but there are judicial review provisions within SBREFA.

MR. VARDON: The next question asks to show a slide again. Any other questions?

This question is for Marie. The results of a voluntary inspection is made at the request of a firm with regional small business representative are said to be confidential. Are these non-regulatory inspection observations reported to other parts of FDA, such as Headquarters?

MS. FALCONE: No, except that if there is an imminent health hazard, then, the visit stops and the small business representative contacts the district, because our job is public safety, but that is a condition for conducting the inspection, and also before doing a visit like that, the small business representative has to contact the district and say, you know, is there something going on. They couldn't just go out there if they are in the middle of a violative situation, so the district gives permission for it.

When I did those, when I was in Dallas, I

was there five years, I didn't take notes and I didn't give a written report. There was no report. I told the company, I had them take the notes, and I had them write down the things that were important for them to know.

MR. VARDON: Thank you.

Are tests required for lead, aflatoxin, and heavy metals?

DR. WILLIAMS: Even though I put that slide up, Karen, maybe you would like to address that.

MS. STRAUSS: Are tests required?

DR. WILLIAMS: Right.

MS. STRAUSS: If they are likely contaminants, they would be required.

MR. VARDON: We don't have more questions.

The next portion of the program is to allow you to meet in small breakout groups to discuss this rule with yourselves, what you think the impact will be to you, to help you formulate your ideas and to talk with each other about ways that maybe you would like to respond.

It is just meant to be a brainstorming session. We would like somebody in each group, we would like you to meet in groups of five or six at

tables that we have set aside in the room adjoining this auditorium, to take notes, if you could find somebody as a recordkeeper to take notes, and at the end of the hour or so, if you could come back here, we would like each of the recordkeepers to discuss what you discussed there.

I think there are 50 or 60 people maybe in the audience or fewer, so I think we can all meet in one room that we have set aside already at the top of the stairs. It is labeled GMP Breakout Session. We will go there and we will ask you to form small groups. We have a facilitator there to keep the discussion focused on dietary supplement GMPs and the impact on small businesses.

I will meet you at the top of the stairs, I guess, in the breakout room.

[Breakout sessions.]

Breakout Session Summaries and Discussion

MR. VARDON: A couple of you have indicated to me that I may have mischaracterized your questions. I thought that we could give you another opportunity to ask them at the microphone. I may have mischaracterized your questions, so we want to give you every opportunity to ask them.

Do we have any volunteers to just tell us

what went on at your table? We do have the transcriber and she will take notes. This will go into the public record, but we hope that this will help us clarify your major concerns.

FIRST VOLUNTEER: The first volunteer for the first table, I guess, or third table, whatever table we were at.

A lot of these are comments, some are questions, so I will just go through them.

One of the first discussions we had was about the heavy burden on the end product manufacturer to test all of the ingredients that are in the dietary supplement, and their inability to rely on their supplier downstream.

A question that arose in that aspect, while understanding the need to be responsible for the end testing, what type of enforcement or inspection does the FDA expect downstream in terms of the suppliers and downstream, particularly when we are dealing with foreign suppliers?

MR. VARDON: Why don't you just finish the whole discussion at your table.

FIRST VOLUNTEER: Do you want me to go through every question?

MR. VARDON: Yes, why don't you go through

everything and then if there are questions afterwards.

MS. ACOSTA: Maybe if you could repeat that first comment now that Karen is here, that would probably be useful.

FIRST VOLUNTEER: The first issue that we discussed in a lot of detail had to do with the heavy burden on the end product manufacturer, the manufacturer that finally finishes the dietary supplement and it is ready to go into interstate commerce.

In terms of the testing requirements for the products, and we are talking about multiple ingredient products, and the fact that there seems to be an inability to rely on the testing that is done by the downstream suppliers, and to ensure the safety of the product throughout the process and to possibly relieve the burden on the end product manufacturer, does FDA intend to have a high level of enforcement and inspection process in terms of the suppliers.

So, in some ways, the intent is to relieve the burden on the end product manufacturer to some extent, recognizing their need to test at the end.

MS. STRAUSS: What we have proposed is the

testing scheme, and this is the proposed rule stage, and based on the comments that we get, we will develop a final rule, and at this point it is difficult to say, you know, the whole CGMP would be required to be complied with, and then an inspector would inspect, and whether there would be greater emphasis on a supplier or a manufacturer of a dietary ingredient or dietary supplement is really, you know, it's impossible to say.

FIRST VOLUNTEER: One question did go to the resources available to inspect foreign sites, because a lot of the botanicals come from outside the country.

MS. STRAUSS: I know I mentioned in my presentation that FDA does inspect materials, they look at materials as they come into the country. If they suspect there is a problem with a particular manufacturer, that has already happened, if they think there is a problem or suspect a problem with a particular supplement or dietary ingredient, they can conduct testing.

FIRST VOLUNTEER: One question concerned small batches, a number of the small dietary supplement companies will have a number of products, that they may run only 100 bottles of a

substance or 25 bottles of a substance, and we wondered if FDA would be considering anything along the lines of an exemption for lower volume of production.

MS. STRAUSS: In the proposed rule, there isn't any exemption proposed for any size, any type of product, any quantity. If that is something that you think should be considered in the final rule, that should be a comment admitted to the docket.

FIRST VOLUNTEER: The next question concerns cleaning issues, validation, or not the validation, but the actual cleaning of utensils and the equipment, and the question had to do with the establishment that the cleaning had occurred appropriately.

Is FDA looking for evidence that the process used will destroy the contaminant, or is the FDA looking for evidence that the process used actually destroyed the contaminant? There are two different questions.

MS. STRAUSS: What we have described and proposed is that it's the manufacturer's responsibility to ensure that whatever process they have developed for sanitation is, in fact, going to

do what they say, as necessary.

So, it's the manufacturer's responsibility to say that yes, in fact, the sanitation process does, in fact, do what it is intended to do.

FIRST VOLUNTEER: So, what I am understanding is that if you use a chemical that should destroy a particular contaminant, and you establish that you used that chemical to destroy the contaminant on the utensil or the equipment, that would be sufficient.

If you use a chemical, if you establish that you have used the chemical in your process that destroys a particular contaminant, that that would be sufficient to establish that you have cleaned your equipment properly.

MS. STRAUSS: And not that you actually cleaned it in your own facility?

FIRST VOLUNTEER: That you used it in your facility.

MS. STRAUSS: But you don't know if it worked in your facility?

FIRST VOLUNTEER: Right, and that is the distinction, the distinction is I have used bleach on this particular equipment as opposed to I used bleach and it killed, I have used bleach and now I

have done testing after the fact to make sure that the bleach killed the contaminant.

MS. STRAUSS: We have not proposed that you needed to do that actual testing, but one would expect that a process used would do what you have intended it to do actually in your site.

MR. VARDON: What I had suggested before you stepped in was that we have just a general summary of the discussion that you had at your breakout tables, and then I mentioned that because I mischaracterized some of the questions, some people didn't feel I asked their questions properly, I would give people a chance to ask their questions again.

Why don't we summarize the discussion first rather than making this a question and answer period.

FIRST VOLUNTEER: Another issue concerned drop shipping, and we are talking about distributors who have no contact with the product throughout the entire manufacturing process. There is no holding involved, it could be an e-commerce site that orders product from another place and it goes directly to the consumer.

There is a question in terms of the

proposed rule and its application to that type of process.

Do you want me to go through all of the issues?

MS. STRAUSS: Actually, this would be a summary of your discussion, so what you are doing, and I guess you started before I was here, so they are going to just give a summary.

FIRST VOLUNTEER: Another clarification that was thought in our group to require some discussion was the need for written procedures, SOPs versus what needs to be in the batch record or the master manufacturing record, the need for SOPs generally was somewhat confusing based on the proposed rule.

The next issue that was discussed was the need or to consider the need for extending the comment period because it is a quite lengthy proposed rule, it has been years since the ANPRM was issued in 1997, and a three-month comment period seems very short for the type of issues that need to be reviewed in this document.

Another issue that was discussed was how a manufacturer developed a testing method for a product where there is no testing method available.

The example given was billberry [ph]. If there is none out there, the question or the comment was based on the proposed rule, it would appear to be appropriate to develop your testing method based on a batch that has come in to your shop or your facility, and base your future batches on that initial batch.

The next issue had to do with the testing. Obviously, testing is a big issue here today. Testing is very significant particularly for the end product manufacturer, and the question had to do with, or the comment, or the expectation would be that testing would only have to involve the dietary ingredients and the lack of contaminants as opposed to going to the excipients that are in the final finished product.

That's it.

MR. VARDON: Thank you very much.

SECOND VOLUNTEER: At our table, we had only one small company manufacturer, that was me. We had somebody from the NIH, from an advocacy group, from a trade organization representing a lot of large and small manufacturers.

We had somebody who was an overseas rep for somebody who wanted to bring products and

traditional Chinese medicine products in, and we had a large company, and we had somebody from the press. So, we had quite a mix there, and we talked about a few I guess more broader issues.

The overseas manufacturer's rep wanted to investigate a little bit more thoroughly about some kind of preview or review. We did indicate that there were wonderful organizations like NSF or private organizations that could help those manufacturers figure out some of these things if they needed that, if we couldn't send our own government people over or perhaps they could investigate funding somebody to go over and visit on a trade mission or something.

We had a discussion of the issue of ingredients like ethyl alcohol, if it is produced by a licensed manufacturer or manufacturer licensed by the government, and they are manufacturing to USP specifications, why do we have to revalidate something like that especially if the vanilla extract people don't have to do that, and they are doing something according--you know, for food GMPs.

We discussed the broad issue that there really must be a way to have some form of a legitimate C of A. That concept has to be made

valid in some way, shape, or form. You know, there has to be a process and verification of batches, you know, that every batch has been verified.

There has to be some recognition other than somebody having to fly out to a facility every single time, you know, if you are buying something from somebody that has had that process validated somehow.

Also, we had a broad discussion on testing requirements, that the language is unclear, and we do need help there. One area discusses about testing finished products, other areas say that you can test your incoming ingredients, and it is really not clear which it is that you want us to be doing.

It kind of seems like there is a choice, but this whole question of validated test methods, I go to all of our industry meetings and we have different classes of goods in our industry, and I think that when you are dealing with what we call the people who are closer to the pharmaceutical industry in their type of goods, they have a different interpretation than people that are closer to the food industry, i.e., tea manufacturers or tincture manufacturers, and there

is no recognition really, and the words that you are using are ending up confusing a lot of us.

The concept that set forth the I.D., purity, quality, strength, and composition, we appreciate that that was broadly worded to take into account a broad variety of goods, but unfortunately, that ends up being ambiguous to us.

I did make the comment that the format that we used in the large group when we kept submitting cards in to you, sometimes our questions weren't clear, and we didn't have the chance to immediately at that point clarify what we meant.

I think maybe in your future meetings, you actually let people get up and give you that question directly because they then have a chance or at least ask them if you have got that question in the context of your answer, because we could get better clarity.

Unfortunately, I also must really ask for an extension because I believe that the Q and A that we had here only gave me greater confusion, not clarity, and this comes at a time of the year where it is very hard for small manufacturers to leave our companies and come here for a day.

I woke up at 3:30 this morning to drive

down here, and I have to get back, and I have to be at work tomorrow, and I am going to get on the phone with some of my other colleagues who are on the West Coast, who are anticipating me coming to this meeting, and we are going to have discussions, but unfortunately, I am not going to be able to give them a whole lot of clarity on some of these things because although I think the format, when we got to actually sit down, it was helpful having Peter there, this still is just we do need better clarity on what you want us to do.

We have been trying for years to kind of figure out where you are headed, you, the FDA, in your regulations, and we have put in laws and processes and procedures. We keep samples. We have been 21 years in business, and what we see, we think, and maybe we are wrong, is a significant increase in the cost of our products.

I am talking for a small traditional manufacturer of tinctures, and we are not really seeing that that is providing a whole lot of consumer benefits. In a recent survey of our doctor and practitioner clients, one of the main reasons why there has been a decrease in the use of botanicals is because they are not covered by

insurance, and they are expensive.

This will only increase the cost on this class of goods, and I really think that when we looked at the benefits and even the risks that were associated in your section where you laid out risks, certain of those risks, very few of them deal specifically with botanical products, so you are heaping the cost of a whole lot of risk.

The two things that I saw were botanical identification in the Digitalis issue, and the ephedra-based issues, which, you know, testing microbial issues are not going to really solve those problems. Those things weren't really appropriate to botanicals.

So, we talked again, and it was helpful, about potentially creating subclasses of goods within this regulatory framework, and Peter was open to that discussion and we appreciate that.

That does create a whole area of important dialogue that would need to take place among some of my colleagues, the small manufacturing companies.

Let's see, excipients were another issue that came up. Reproving already proven items that are used in food, there is no grandfathered type

concept. These are things that we have been using for a long, long time.

We had that grandfather concept with dietary supplements themselves, why not with some of the ingredients that are already being used in this class of goods and are being used in foods, why must we reprove these issues.

We believe that your estimates of cost are extremely low, and we think they will be much higher, but we don't really know because of the issue on lack of clarity. The difference between the preamble itself and the regs, the preamble, we hope you just discard that, and we deal only with the regs, because it is in the preamble where a number of concepts that are introduced that really confuse the issues that I think the regs are trying to get at.

The concept of validating certain processes was raised at our table, and I think that this is a constructive one. For example, if alcohol is used in processing tinctures, if we can validate that really there is no microbial growth at all in the finished product, that should obviate the need for having microbial testing. So, that would be a process validation.

Similarly, soil tests with certified organic cultivation may be another process that would get around the need for heavy metal testing and lead testing in every single product.

We talked about the issue between training and experience or training or experience, and we really wish you would give that "or" back in there, because we have so many wonderful people in this industry who just didn't go to school to learn what they did.

They learned with traditional healers, they have learned by self-study with amazing books and texts that are available, they have learned in clinical practice in working with practitioners, and we believe that you should honor that tradition by putting that "or" back in there.

We also really would like you to correct the impression out there that we think is awfully unfair in some of your press releases, that there is no regulation of dietary supplements. You said it yourselves today that we are subject to the food GMPs right now as they exist.

You know, the FTC, if we don't put on our label what is in the product, that product is adulterated. We are supportive in trying to make a

quality class of goods here, but I think one of the big issues for us is that we don't want to overburden people who are making high quality products, people that have been in business 20, 30 years, that we can parade a whole list of people in here to tell you that our products do work, and we are trying to maintain their affordability for people.

We are just saying that you need to perhaps tailor some of these concepts for the broad class of goods that we have in our industry.

Thank you.

MR. VARDON: Thank you very much.

Anyone else?

THIRD VOLUNTEER: I will go over the points that we talked about at our table. We talked about recordkeeping in regards to the maintenance records, environment control records, cleaning records, that the requirement now appears to be that they would need to be copied into multiple batch records, that you can keep a logbook, but you must also keep those with the batch records.

The question was raised why can't they be kept separately on logs, making one copy rather

than copying that 50 times and inserting them with every batch record.

Also, although there were some written procedures that were not required, clearly, they are going to be needed to be done anyway, SOPs or training records, there is many procedures beyond the written requirements. Just to employ those with the other ones, that will have to be done in order to accomplish the ones that are required, so that was thought to be a cost issue that was not captured, that there are hidden implied requirements, such as SOPs.

Sampling of finished products for testing, how many would need to be tested? Right now there is not a need for process validation, but it must be adequate and suitable. Without a process validation, how does one determine what is adequate and suitable?

We also discussed about method validation and wondered why validated methods need to be revalidated or re-re-re-re-validated as it is done in every single company that would use them. It is not just finding that it fits the purpose, but indeed it sounded as if that a full-scale revalidation, a full-scale validation of the

methods had to be done in every lab, and that is not currently a drug requirement.

Also, on cleaning, the question was raised how does one validate a 5-log reduction if the surface already is clean, if you don't have 5 orders of magnitude of microorganisms to kill off, you are then bringing microorganisms into your facility to show that you can kill them?

It sounded from the discussion earlier that if you are using bleach, and it is known to work, you don't actually have to demonstrate a 5-log reduction, but that wasn't clear I guess from the reading of the proposed rule.

Also, we had one other thing between drug GMPs and the proposed dietary supplement GMPs, that a lack of being manufactured to GMPs would render the dietary supplement as adulterated.

That is true for drugs, but it is not a food requirement. This could present particular issues for companies that sell their finished product that becomes the raw ingredient for food companies or dietary supplement companies.

If you make an enzyme product, for example, a food company may be buying that if it is pure, clean, has the adequate strength,

composition, that is accepted as food, however, if it was not manufactured according to the dietary supplement GMP, and they also sell the dietary supplement ingredients, then, that would be subjected to recall.

So, it was thought that that perhaps may be not the best way to have that simple recall ability just because it didn't meet GMP, and when, in fact, it is clean and pure and meets composition requirements and label claim.

There were a couple of boundary issues of sellers of bulk herbs at the retail level as to when those become dietary supplements. I think it was thought that this one it is labeling, but if it is determined that a bulk herb in a jar is labeled and becomes a dietary supplement, how retail is affected and what GMP requirements did they then have to meet for consumers that can come in and scoop out herbs and put them in a bag, weigh them, and take them away.

So, will retailers need to make special requirements to ensure that what they are selling at that level is regulated as food, and not dietary supplements, that someone can buy their spices, but right next to it, if it says echinacea helps

promote healthy immune system function, when there is that labeling them under dietary supplement, and retail has become subject to GMPs for dietary supplements.

We also had the question if dietary ingredients were grandfathered in DSHEA, why not dietary components, such as the excipients, why does methyl cellulose have to be determined to be GRAS at each individual facility.

It seems that excipients were not grandfathered in as the dietary components, that they need to be proven GRAS status even though they may already be generally regarded as safe, but not given any official recognition as that. It seems to be the burden is on the manufacturer to prove that.

Also, the line between raw agricultural commodities and dietary ingredients, what definition will be employed there? It seems that that is an important one to figure out for several reasons, some of which we did not actually get into at our table.

For the very small companies, say, the tincture manufacturers, that at least special guidance is required for them. Peter, I am glad

that this issue was brought up for you, because it is clear that you could almost carve--the dietary supplement proposed regulations were made apparently, they certainly are adequate for the very large companies.

If you were to start over and pretend you were doing it only for those tincture manufacturers, what would that guidance look like, and what would those look like, would it be responsible and would the public interest be secured, do any changes need to be made in the proposed rule, in other words.

At the very least, guidance, and do we really have adequate input. I think if we talk about small companies that are in danger of going out of business, they probably are the people who have been doing this traditionally, and I think that is something that much more input is required.

I think that is about all that we covered. Those are the major points.

MR. VARDON: Thank you very much.

I think there should be one left.

FOURTH VOLUNTEER: I won't go over the stuff because I think everybody hit on all the high points, but we did have one additional question

that did come out of our group, and I guess this would be like a two-part question.

Is a small business defined based on corporate entity size or business entity? For example, if a dietary supplement business entity is less than 500 employees, but the corporate entity is greater than 500 employees, is it a large or a small business?

MR. VARDON: I think that would be a large business. There is no practical difference. It is only an analytical device for us. I guess the practical difference is when you have to comply with the rule, and that is what you are wondering about.

FOURTH VOLUNTEER: Right.

The secondary question off that was is there a secondary method for establishing a small business entity, such as based on annual dollar sales?

MR. VARDON: No, we just look at the number of employees.

FOURTH VOLUNTEER: The rest of the information was really covered by all the other groups, and it would just be redundant to repeat it.

MR. VARDON: Well, this has been helpful for us. It has certainly been helpful for me. I know there are passionate feelings about this, so we do want to impress upon you that this comment period really is something that we are taking very seriously. It is not just something perfunctory, it is not just something that we are going through. We are not just going through the motions. We really are listening to you.

So, I hope this will help you formulate your comments, so that they can best help us improve the rule. I know a couple of you did have questions still, and I will give you another opportunity.

MS. STRAUSS: I would also suggest that if you have a question on a particular requirement that is in the proposed codified, that you go back through the document and locate, even search using PDF for that particular codified number, so that you can see how we discuss that in the preamble, because many of the questions that were asked, although I will admit that this document is very technical and clarity is very important and sometimes in the writing and in the reading, there is a disconnect, but I would say if you are

concerned about a particular requirement, go back into the preamble and read what we have written there about that particular requirement to give some interpretation to it as part of your sending a comment to us, so that you can kind of get a sense for where we are coming and then comment on that, so we can know that you know what we have proposed, because some of the questions are not quite consistent with what we have discussed in the preamble, and I think that would be helpful to both of us as we get your comments and read them and then go through and do a final rule.

But this has been very helpful especially in the areas where there isn't clarity and when you give flexibility and try to describe that in words, it does get a bit confusing, I will admit, so your help in getting clarity is very important.

MR. VARDON: Do we have any questions, last questions?

If not, I hope you will come to our events in the next couple of weeks.

Thank you very much.

[Whereupon, at 4:00 p.m., the meeting concluded.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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