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ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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SITE SPECIFIC STABILITY SUBCOMMITTEE

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Wednesday,

September 22, 1999

The meeting took place in the CDER Advisory Committee Conference Room, 5630 Fishers Lane, Rockville, Maryland at 8:30 a.m., Steve Byrn, Ph.D., Chairman, presiding.

PRESENT:

STEVE BYRN, Ph.D.	Chairman
KIMBERLY LITTLETON TOPPER	Executive Secretary
LEON LACHMAN	Academic Representative
GARNER PECK, Ph.D.	Academic Representative

ALSO PRESENT:

BILL BRADLEY	Industry Representative
ROBERT KASUBIK	Industry Representative
KAREN MALIK	Industry Representative
SCOTT REYNOLDS, Ph.D.	Industry Representative
ERIC SCHEININ	FDA Representative
ROBERT SEEVERS, Ph.D.	FDA Representative
ROGER WILLIAMS, M.D.	FDA Representative
CHI WAN CHEN, Ph.D.	Working Group Member
ANTON H. AMANN, Ph.D.	Public Comment
TOBIAS MASSA, Ph.D.	Public Comment
SEAN BRENNAN, Ph.D.	Audience Comment
BOB CLARK	Audience Comment
COLIN GARDNER, Ph.D.	Audience Comment
BOB JUERSSI, Ph.D.	Audience Comment
BOB POLLOCK, Ph.D.	Audience Comment
SUVA B. ROY, Ph.D.	Audience Comment

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(8:35 a.m.)

CHAIRMAN BYRN: Good morning, everyone. I'd like to call this meeting to order. The order -- the early order of activities is that Kimberly Topper is going to read a conflict of interest statement, and then we'll introduce the members of the committee.

MS. TOPPER: The following announcement addresses conflict of interest with regard to this meeting and is made as part of the record to preclude even the appearance of such at this meeting.

In accordance with 18 USC 208, general matters limited waivers have been granted to all committee participants who have interest in companies or organizations which could be affected by the subcommittee's discussion of the March Site Specific Stability Proposal from the Agency and the public comments submitted to docket 98D362.

A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office in Room 12A30, Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

There is a couple of administrative things. We have new microphones. All you have to do is press the button and it will be on. If it's red, you're live. Please make sure you speak directly into the microphones. Press the button and it will go off.

CHAIRMAN BYRN: Okay, let's go around and introduce ourselves.

My name is Steve Byrn. I'm a Professor and head of the Department of Industrial Pharmacy at Purdue University.

MR. LACHMAN: I'm Leon Lachman, Lachman

Consultants Services.

MR. SHEININ: Eric Sheinin, Office of Pharmaceutical Science, FDA.

DR. SEEVERS: Bob Seevers, Office of Pharmaceutical Science, FDA.

DR. WILLIAMS: Roger Williams, CDER, Office of Pharmaceutical Science.

MR. BRADLEY: I'm Bill Bradley, Vice President, Technical Affairs of the Consumer Healthcare Products Association.

DR. KASUBIK: I'm Rob Kasubick representing the generic industry.

DR. REYNOLDS: I'm Scott Reynolds representing PhRMA.

MS. MALIK: Karen Malik representing HIMA.

DR. PECK: Garnet Peck, Professor of Industrial Pharmacy, Purdue University.

CHAIRMAN BYRN: Okay, as you can see -- did we hand out an agenda to the -- as you can see from the agenda, the plan is to have some presentations from the committee members. I want all committee members who are not listed to realize that if you would like to make a

presentation, we can include you after Scott Reynolds' presentation.

We'll then have committee discussion and proceed through -- and then have an open public hearing, followed by a discussion of approaches to resolution of the issues brought up.

So I think we can begin with Bob Seevers from the FDA reviewing the questions and discussions from the last meeting.

DR. SEEVERS: Good morning. Everybody got me in back?

It's good to be here, particularly because the participants have worked hard to come to some sort of consensus about what's been a very controversial issue.

Kimberly, if I could have the next overhead, please.

This is a very brief history. If you look at the 1987 stability guideline, the red book from the Agency, you'll see that the concept of site specific stability is present; but over the years, it's been implemented by the Agency in a very inconsistent manner.

What we tried to do in the draft domestic stability guidance that was put out in June of 1998 is provide a framework for a consistent regulatory policy on site specific stability. There were a number of stability guidance comments related to this topic.

I think it's safe to say it's the one most discussed, most concerned issue in the stability guidance. In July, we had a meeting -- July of '98, after the guidance came out, we had a meeting on site specific stability.

We presented the proposal in the draft guidance. We heard from a number of interested participants from industry, who raised a number of concerns. As I said, the guidance received a number of comments.

On February 3rd of this year, we had a pre-meeting with the academic experts who are members of this subcommittee to bring them into the loop on this issue. On the 29th, we put out a draft tiered proposal for site specific stability.

And on the 31st of March of this year, we had our previous subcommittee meeting, at which a number

of presentations were made. We then reopened the guidance for comment so that anyone who wished to comment on this issue, or indeed any other, could address that.

Overall, more than 60 entities, corporations, individuals and trade organizations commented on the guidance. In my office, you will find what amounts to a ream of paper just of comments. When we organized that by specific comments addressing individual issues, there were nearly 3,000.

The stability committee, of which I am chair, is currently engaged in making revisions to the guidance based on the comments we've received. All aspects of the guidance were covered.

Now let's talk a little bit about what we heard from the public on the site specific stability issue. The comments break down into four basic areas: the regulatory basis for site specific stability, the scientific validity of requiring site specific stability, the logistical and economic concerns of the pharmaceutical industry if the proposal either in June of '98 or the revised March 31st, '99 proposal were implemented, and technical aspects of it.

If I could have the next slide, we'll share with you some of the scientific comments that we heard.

One thesis presented to us by a number of commenters is that stability is intrinsic to the drug product; and therefore, site specific stability would not be necessary. I presented a number of examples at the March 31st meeting which the Agency has seen over the years indicating that that's not universally true, that there can be problems.

I'll come back to those examples, without going through them again, later in my talk.

The main message that we heard from industry is the second bullet point here, that process validation and technical transfer, when done correctly, provide sufficient assurance that the product made at the new site will be the same as the product made at the pilot site.

We heard the concern that a site change is less critical than a scale up at the same site, but no additional stability is required by the Agency for scale up up to a factor of ten. We also heard that site specific stability should not apply to drug substances.

The regulatory comments we heard can be summed up on this slide. First, it's contrary to or goes beyond ICH or the spirit of ICH. The Agency understanding of ICH Q1A has been that topics not addressed there were not addressed for a couple of reasons.

One, because they did not come up in the drafting of the document. Or two, because they did come up and a consensus among the ICH parties could not be achieved. That being the case, the Agency understanding has been that where ICH is silent, the domestic regulatory agency can set policy, and we feel that's the case here.

We have heard that site specific stability is inconsistent with what is in FDAMA, specifically where FDAMA says that we can approve based on pilot data. And the Agency agrees that we can and would approve a new drug based on pilot data -- we do that -- but that what would be approved would be the pilot site of manufacture.

FDAMA, similarly to the ICH situation, does not address what data would be needed from the commercial site. Similarly, the theory behind ICH, and behind the

domestic guidance I would say as well, is that we're looking for a conservative expiration dating period.

We want the drug to be good at the end of its expiration dating period and it doesn't suddenly turn into a pumpkin at midnight on that date. Therefore, if there is a minor concern about stability due to a change of site, the conservative expiration dating period would take that into account and allow for a little wiggle room, if you will.

Let's talk about what we heard in terms of the logistic, economic and technical issues. Site specific stability submission in the NDA is burdensome to industry. This was said over and over again. We had recommended, both in the '98 draft and in the '99 tiered proposal, that for complex dosage forms three batches of site specific stability be submitted.

This was viewed as excessive. The term "intrinsically unstable" and "complex dosage form," both of those terms need to be clarified. And I would agree with both of those comments.

Over the summer, in two different individual new drug applications, we received from two different

firms alternative proposals to site specific stability. In neither case were these proposals submitted to the public docket.

What I am going to talk about here is not proprietary information; however, the submitter of those NDAs and anything connected with them obviously is. The first proposal as an alternative --

DR. CHEN: I just want to make a correction. These are not already NDAs. They are pre-NDAs.

DR. SEEVERS: Thank you. That's Dr. Chi Wan Chen, who received -- whose chemistry division received this communication from both firms. This was a pre-NDA communication. I apologize for the error.

But as in all of the guidance policy, we are open to valid alternatives. If a firm can present an alternative to what we've suggested in the guidance is necessary, we are open to that. And taking advantage of this policy, these two firms presented alternatives.

The first proposal was the following. The firm would submit full ICH data on a combination of two primary stability batches made at the pilot site and one batch made at the commercial site, and they asked would

that satisfy our need for site specific stability.

The second proposal made the following suggestion: that instead of submitting site specific stability proapproval, the release data on the three validation lots made at the commercial site would be submitted, plus a summary of the validation process; would that be acceptable.

We spoke with this firm. And let's go to the next slide. I have something on the bottom of the current slide. This slide spells it out in a better fashion.

In each case, we spoke to the firm and said that in those specific instances, the proposal had merit, we would look at it further, but one assumption had to be made.

And that's key to the discussion that we're going to have today. That assumption is the following. If we're going to look at any alternative to site specific stability data for new drug applications, the firm must have an adequate primary stability data package.

The question is: how do you define this?

Fortunately for us, that work has already been done. Industry, and the Agency, and the USP, and our international partners in Europe and Japan have already agreed on what is an acceptable primary stability data package.

That is 12 months on three batches at 25 degrees, 60% RH; six months on three batches at 40 degrees, 75% RH.

I want to emphasize that this assumption underlies any discussion that we have this morning that if those data are available at the time of submission, then alternatives to site specific stability may be workable.

Last slide, please.

And so the question that the Agency is posing to the subcommittee for discussion today is to discuss the merits of the proposals. The third proposal, which I have not spelled out in great detail, is in the meeting package, is the three tiered proposal from the Agency.

So we have three proposals: the site specific stability proposal from March from the Agency,

the proposal to use a combination of pilot and commercial site batches, and the proposal to use release data on validation lots and a summary of the validation process.

That being said, I look forward to the discussion today.

Thank you.

CHAIRMAN BYRN: Okay, I think we can go ahead. Unless there are specific comments or questions for clarification for Bob, I think we can go ahead with Scott's presentation.

Any specific questions for Bob?

MR. LACHMAN: Bob, are you covering ANDAs in your summary here or just the NDAs?

DR. SEEVERS: At this point, my view is that what is currently submitted three months on one batch accelerated for ANDAs represents the primary stability data.

MR. LACHMAN: All right.

DR. SEEVERS: And as I said, that the primary stability data is essentially nonnegotiable for NDAs, that would stay. In the event that an ANDA submitting firm wished to change its commercial site

before approval, something that can happen but is extremely rare, then one of these alternatives might be useful.

MR. LACHMAN: Okay, I just want to get that clarified.

CHAIRMAN BYRN: Any other questions for clarification?

Okay, Scott.

DR. REYNOLDS: Good morning. I'm representing PhRMA with a summary of some issues on this site stability issue.

In the first slide here, I've just recapped the proposals that I believe we're here to discuss. What I'd like to do today is briefly recap a few of the issues that we discussed in the March meeting, particularly those that I think are pertinent to a compromise position that PhRMA is proposing to try and address this issue.

But, as was discussed just a few minutes ago, the three proposals are the original site stability plan; the second is what I would call a hybrid plan; and the third being the plan with some release data and summary of validation process with the caveat of the full

ICH package to accompany that.

And the following slide is just a summary of the issues that we discussed at the March meeting, which -- and that is that the primary issue that we were trying to tackle really was one of ensuring successful technology transfer, and the question was how do we best do that.

And what we presented was that this requires several things: a thorough process development experience, evidence that the design and operation of the manufacturing plants conform with GMPs, and a demonstration of process robustness through process validation in the final manufacturing plant at final manufacturing scale.

And the other comment, of course, was the one that had been made to the docket by many of the firms, is that the value of site stability just hasn't been demonstrated to provide that assurance, and there's a better tool, and that tool is process validation.

In the next several slides, again I want to just emphasize how validation is linked to other activities that go on in the course of drug development.

We discussed that process development is continuum; that this relies heavily on laboratory work, subsequent pilot plant work, and finally work that goes on to take that process out of the manufacturing plant.

And during that continuum of process development, the formulation composition is determined, the processing conditions are established, the environmental control conditions that are necessary in the manufacturing plant are established, and this is all done during this process development phase.

The key here is, of course, that during that development phase is when this process validation exercise actually begins. That's when the process and equipment conditions are established to ensure that we have robust manufacturing conditions.

That's when we begin to identify the critical quality attributes of intermediate products and the final product.

It's also during this process validation phase that we begin to identify and define critical process parameters, the in process controls, those that are established for regulatory purposes, those that are

internal to the firm to ensure that they control every step of the process, and these all form the basis of these scale up plans and the process validation exercise.

Now the last point on here is really the key point, I think, for discussion here, is that it's really the link between that process development and the validation plans as they're reviewed during a proapproval inspection that is most important to understand.

It's the development exercise, the GMP aspects of the plant and the validation plans all are reviewed as a single package, and that's where the most benefit can be achieved.

So I'll briefly go through the PhRMA comments on the three options and try to end here with a -- what we feel is a significant compromise to try and arrive at something that will provide the best possible tool, but also provide the best vehicle for providing that evidence of successful technology transfer.

The first option that was discussed was site specific stability, and our response is the same that we presented in March: site specific stability is not the

best marker; we're not answering the right question with the best possible way; and that the best tools for success include, as I mentioned earlier, thorough process development, adherence to GMPs in the manufacturing plant, and completion of process validation in that manufacturing plant.

The second option we have basically the same comments and also again a comment that the commercial burden to the firm really isn't removed with that option. So I think we quickly move to the third option.

Now the option is presented. It's to provide release data on three validation lots made at the commercial site, plus a summary of the validation process the firm submitted that full ICH program in their stability package.

PhRMA agrees with the release data on three validation lots in the form of a certificate of analysis, and that this would be submitted prior to the PDUFA data.

I'd like to go to the last slide here and just summarize this.

So, in summary, the PhRMA proposal is to

confirm the completion of successful technology transfer with that certificate of analysis of the release data on three successful validation batches, and that would be done prior to the PDUFA date.

Most importantly, we would continue to rely on the existing systems of proapproval inspections to ensure that that process development, the GMP stature of the manufacturing plant, and the process validation in that manufacturing plant are all properly reviewed.

And this should provide everything that we need to have here. We need to hang our hat on something that says we've got good technology transfer. We've got the certificate of analysis to certify that those validation batches were carried out and here's a piece of data that's easy to get our hands around, the release data on those three validation batches.

And we use the existing framework within the Agency that works within the industry as well to make sure that that validation as completed is linked properly with the plans of the plant, the manufacturing status at the plant, and the process development experience at the plant.

And that's done now, and we propose we continue to use that mechanism to review the details, those nitty-gritty details we got into a little bit back in March, to truly review all the details of process validation.

So that was the completion of my presentation. I'll be glad to answer any questions.

DR. SEEVERS: Scott, I notice a difference between what you were saying makes sense to PhRMA and the third option as I presented it, which is as we received it in the pre-NDA package from one individual firm.

DR. REYNOLDS: Right.

DR. SEEVERS: And what's missing, of course, is the quote, unquote, "validation summary."

DR. REYNOLDS: Correct.

DR. SEEVERS: Could you comment on that, please?

DR. REYNOLDS: Yeah, I'm sure that -- and different firms can approach this in different ways. The key issue here from the PhRMA perspective is that across the industries that we represent it's -- one, it's not reasonable for every industry to be able to do that.

And secondly, from the PhRMA perspective, we feel that we're much better off relying on the existing framework that already exists from -- within the field to review the details of process validation. We feel that we can provide that one piece of pivotal information in terms of the release data on those validation batches, and that provides a good, simple, streamlined framework to make this happen.

Individual firms can certainly come up with embellishments upon that, and that's fine; but as a solid baseline that PhRMA felt comfortable with, this seemed to be the most appropriate way to manage that.

DR. SEEVERS: So PhRMA is agreeing with the third option minus the validation summary, but including primary stability data?

DR. REYNOLDS: That's correct. I'd say it's actually a little stronger than that. I'd say PhRMA is agreeing with this validation data -- excuse me, with the release data on the validation. And PhRMA emphasizes the fact that the details that would be provided in the summary validation are there to be reviewed as part of the proapproval inspection and as part of the ongoing

interactions with the field.

And so I think we're trying to emphasize that the whole package is there and we're trying to make sure that the parts of the package are deployed in the areas where all the skill sets are there and where things work right now.

DR. SEEVERS: I want to thank you for the misstatement you just made because it's one I've made before talking about validation data instead of release data on validation lots. In our internal discussions in the Agency, we've had to learn to speak very carefully and slowly because what we're not talking about -- and I want to make this clear to everybody here -- is validation data.

That's already being reviewed by the FDA field inspectors and there's no need for the center reviewers to look at those data. We're talking only about the release data, the certificates of analysis. And so you made the same trip that I've done many times, and I think it's important that we all agree and understand that that's what we're talking about. It's the release data.

DR. REYNOLDS: Correct.

CHAIRMAN BYRN: Okay, thanks very much, Scott.

Any other questions for Scott?

MR. LACHMAN: Scott, normally you'd have a validation summary for your three validation batches, isn't that correct? You would summarize the validation data in the summary report.

DR. REYNOLDS: That would be -- I'm not quite sure I understand the -- it would be -- certainly there's a detailed validation report assembled by the firm, and that's done at the conclusion of a validation exercise.

MR. LACHMAN: Yes, but generally there's an overall summary of the validation? You know, the individual validation data could be cumbersome many batches, many folders, and then there's an overall summary of the data.

DR. REYNOLDS: I don't --

MR. LACHMAN: Executive summary.

DR. REYNOLDS: I mean, like any good report, there's always a summary section. Whether that summary

section includes a -- well, I would say I don't believe that summary section includes a standard assembly of validation data primarily because, as you said, it's a complicated collection of data.

And to have a codified mechanism to cull out the critical parts of that just doesn't exist right now. And that's really one of the reasons for being concerned that, in a general sense, across the PhRMA companies, that we could come up with a consistent, codified way of presenting every part of that validation summary.

I don't think there exists a consistent mechanism for providing that summary data.

MR. LACHMAN: Well, I think you can develop a framework depending on a dosage form whether it's an injectable or an ointment or a solid. You can have a structured summary if you want to do it.

DR. REYNOLDS: Perhaps, but I think it's more complicated than that because I think, you know, a good validation exercise which really -- and we talked about this in more detail last March. A good validation exercise that really goes and probes the nuances of the process really builds on all of the work that was done

during development.

So I think even within certain dosage forms, you'd find nuances of formulations, composition, process conditions that a firm would perhaps want to probe in their validation exercise which would not be necessarily consistent even across dosage forms.

Now, those details are looked over in detail during a proapproval inspection and in subsequent reviews of validation at the site. But they're not necessarily -- my experience has been that even within dosage forms, there's a fair variety of complexity.

MR. LACHMAN: No, that's true, but generally I see summary reports with the validation which the field looks at, not the reviewing group. Reviewing group doesn't look at the validation.

DR. SEEVERS: I think the question that we as a committee need to address in the sense of the summary is how much value does it add to the review process in the center, not the field, to have the validation summary in addition to the certificates of analysis.

And I'd like to hear what the different

members of the committee think about that.

CHAIRMAN BYRN: Maybe we go back to Scott. I think what Scott was saying was that the PhRMA position is that this is already reviewed by the field. Is that --

DR. REYNOLDS: Yes, that's correct. I think Bob's question is right on the money, what is the value of that. And it depends on what we're trying to find out here. But if what we're trying to identify is did the validation get done and show us an easy to find collection of data that we use to just hang our hat on.

And that is here's the release data from our validation lots, here's a certificate of analysis that says these are from three successful validation lots, and the center is assured that the validation was carried out.

Now, beyond that, the next step is into a fairly high level of detail, which is the details of the process validation work. To cull that out and -- I think would be difficult to do. And I don't know if that would truly be a value.

Since the detail work with the whole context

of the plant and development work is already being reviewed, I don't know if that really adds value to the overall process as long as there is clear assurance that that validation was carried out and some simple and easy to codify collection of data associated with that and the release data seem like the most appropriate collection data to do that.

DR. KASUBIK: Yes, I believe, speaking for the generic industry, that they would go along with that in saying that since it's already being done at the district level for the inspections, resubmitting it again really wouldn't generate anything extra for assurance of the process.

DR. SEEVERS: So what I hear both of you saying is that the certificates of analysis, by themselves, would serve as tokens, if you will, demonstrating the process validation has been completed successfully; and the actual release values of the specific specifications could be compared to the release values of the pilot data to show the sameness, is that correct?

DR. KASUBIK: Yes.

DR. REYNOLDS: Yes, that's how I see it.

CHAIRMAN BYRN: One question in the C of A's, of course, is are the -- how are the specifications determined, are the critical specifications on the C of A? Without a summary, the assumption -- that would be assured under this -- under the PhRMA scenario, that would be assured by the field.

DR. REYNOLDS: Actually, the release data from the validation lots would be the same criteria that would be applied to the product, and the justification for those would be already have reviewed through the NDA.

So this is simply comparing the release data on those validation batches to the release data -- to the release criteria that would be established in the NDA. And any discussion about the justification for that would be -- would have been established as part of the NDA.

CHAIRMAN BYRN: Okay.

DR. SEEVERS: You need to have a target to aim at, and the release data can help set final specifications if there's any disagreement between the Agency and the firm. As sometimes happens, the Agency will recommend a tighter specification, for example, on

an impurity, and a firm often says wait 'til we make some batches at the commercial site before we tighten this as far as you want it to go.

Right now, the specifications are being set based on the pilot data and the pilot stability data. Having these certificates of analysis in hand would be an advantage in setting data based specifications for a drug.

So I see that as one advantage of this proposal. Those times when it's difficult to set the final range of a specification, this would provide additional data to the center reviewers to work with the firm to come up with a usable specification.

MR. SHEININ: When you're doing the validation studies during technology transfer, are the validation batches consecutive batches or can they be three batches that just happen to meet your acceptance criteria?

I think I've heard that. If I can remember correctly, the validation batches have to be three consecutive batches. Is that always true?

DR. REYNOLDS: I'm not a complete expert on

the -- every regulatory aspect of the validation work. I know that the guiding principle is that the process has to remain in control through the course of the validation batches. So that if a hurricane hits in between batches two and three and there's a problem -- I'm being facetious.

But I think the issue -- the process has to be under control. And so, and clearly running, you know, 20 batches and picking out three that work I don't believe would ever be accepted as showing the process is in control.

So that's all I could really say. Whether that -- the nuances of what makes things consecutive or not I'm just not in a position to comment on.

DR. KASUBIK: I believe, just to comment on that, the intent is to provide three consecutive batches unless there was some reason, you know, a reactor would break down, and then obviously that batch is not considered as one of the consecutive ones.

But the intent is to have three in a row.

MR. SHEININ: And in general, can you -- I'm sure there's no standard number of batches that you're

making, but I would assume that you just don't go in and move this process into your commercial facility and the first three batches that you make are your validation batches.

Is that a correct assumption, that there may be a number of batches that you make before you're able to get three consecutive batches that are meeting all of your acceptance criteria? Or would it be fair for you to say there are times when you just go in and you set up your equipment and you test out your equipment and the first three batches that you actually make meet the criteria?

How often do you think that would happen?

DR. REYNOLDS: I think there's a mixed practice that exists there partly because of the mixture of complexity of processes. And I think firms sometimes conduct specific trials of particular parts of a process that they think needs to be studied most effectively.

I think also some firms may elect, if they think it's overall a complex process, to try and study the entire process in its entirety prior to setting the criteria that they'll use to go into their validation

exercises.

But I think it's a mixed practice and it depends a lot on the strength of their own development work, how confident they are in the scale up. And it really is, I think, a mixed practice. But I don't think you could say that it's always at either end of that spectrum.

MR. SHEININ: Would it be fair to say then if you did try to prepare a summary of what you did during validation, it would include successful runs as well as what led up to it and maybe unsuccessful runs as well?

I mean, those kind of data I think probably would be helpful to the reviewers taking a look at the certificates of analysis given that, if we accept that proposal, there would not be site stability from that site up front.

DR. REYNOLDS: My experience in proapproval inspections and discussions with the field is that very topic is discussed in great detail. And any scale up work that was done in the plant, any failures during that scale up exercise are subject to a fair amount of

discussion and scrutiny.

So again, I don't -- and so that information is reviewed as part of that whole continuum of development and process validation. That's been my experience with field investigators during a proapproval inspection.

So in that forum, I think it is reviewed in quite a bit of detail.

DR. SEEVERS: Can I ask the committee a general question? Because we're getting into some interesting details here. There's three different proposals here and we're getting into a great amount of detail about the third.

Does the committee feel that the merits of the first two proposals, relative to the third, are such that we should spend more time discussing the third? Is there anything we need to talk about there or should be just dive in? That's -- which we seem to be doing.

CHAIRMAN BYRN: Yes, I think this is -- maybe we should step back for a minute and look at all three proposals and see if there's discussion on the first two. If there's no further discussion on the first

two, then we can go back and discuss the third proposal.

We got into this because we were trying to clarify some points that Scott made and now we're getting into the details. So if there's no objections on the committee, let's step back and let's hear any comments on the first proposal, which is the original three tiered FDA proposal.

Are there any comments that anybody would like to make on that proposal? Maybe I should say is there any support for continuing to investigate the merits of that proposal or can we consider that the committee has lost interest in that proposal, if you will?

DR. SEEVERS: From an Agency perspective, one thing that I think we would like to see -- as I said in my presentation, a guidance offers suggestions as to the types of data and the timing of data to support new drug applications and changes.

I think that if we all agree that PhRMA's proposal is the way to go in that event, there still is going to need to be some alternatives. And what I would like to suggest to the committee is that the Agency

proposal from March may serve as an alternative if we go in that direction.

We still feel that that has validity and may make sense in terms of the needs of some specific applications. We feel that the data that we've requested in that proposal would be adequate to support the new site.

CHAIRMAN BYRN: Okay, so let's discuss this option which Bob is proposing. Now, one scenario would be to go ahead and rule this out as a primary option. And we have two alternatives. One is to discuss this option now, to assume that this will not be our primary -- a primary alternative, but it would be an alternative in some future guidance.

Maybe we can just go ahead and discuss that now. So the question on the table is what does the committee think about the merits of the first proposal being a primary -- an alternative to some other option in a guidance?

Maybe I can just say so you're proposing, Bob, that if people -- if one or the other two alternatives were accepted as the main alternative, that

people would still be allowed to follow the original Agency proposal, the three tiered proposal, as an alternative?

DR. SEEVERS: That's right, because we'll get more into this with details. For example, not every firm right now is doing validation before approval. And it may not be possible for firms to do validation before approval.

For a particular case, the time line involved in the three tiered proposal may be advantageous to them. The Agency is not saying that we no longer believe the data we're requesting there are adequate to support this.

So yes, I think it would be a worthwhile alternative.

CHAIRMAN BYRN: Discussion.

MS. MALIK: Speaking from a HIMA perspective, I think -- and I certainly understand why it might be important to retain that as an alternate mechanism. And I think certainly there will be times when either there's limited data available or there may be some questions about a process validation or a

technology transfer where you may want to reserve that.

I think leaving that in as an alternate, I think there were still some comments in terms of categorization, but I think those could be -- those get into the details and perhaps could be worked out, just as some of the details about the third proposal.

DR. SEEVERS: And we do have those comments in the public record. And if that is adopted as an alternative, those comments will be taken into account and any revisions that we feel are appropriate would be made.

DR. REYNOLDS: Yes, I think in discussions that I've had with the industry group that I represent, I think we could certainly accept the two choices of an alternative. We'd want to have that choice that the firm could make.

And I think an additional comment is, with regard to complexity, is there's different ways to look at that, but one way to look at that is to say that actually the complex processes really do require the complex analysis that process validation provides.

So there's several ways to look at that

complexity issue.

MR. BRADLEY: I think it's in keeping with the concept of a guidance to have alternatives. Guidance is not considered binding on either the Agency or the industry, but it does give guidance, as the name applies.

We would certainly not object to having alternatives. What we would object to is having a requirement that we would feel is not suitable. So if there are to be alternatives, then it comes down to a discussion of how to craft those alternatives so that they are acceptable.

DR. KASUBIK: Yes, I believe I can go along with Bill in saying that, in a previous comment, that some of the definitions of what constitute moderate and minor certainly need to be clarified and rethought.

But the general idea of having that as an alternative would be fine.

DR. SEEVERS: I agree with you. And as I said in my presentation, we recognize the fact that we did not provide sufficient information in the '98 guidance as to the issue of complexity. We tried to be more specific in the March proposal by putting basically

as many dosage forms as we could on there and saying if your dosage form is this one, this is the route that you would want to take.

Let me note for the record, and Kimberly I'm sure will correct me if I'm wrong, while the official comment period is closed, the docket still exists. And if you submit a comment, we will receive it and, given whatever time constraints we have, do our best to take it into account.

So if you have not yet commented or, on the basis of today, feel that you need to add a comment to the public record, that option is still open. If you submit a comment, we will receive it and do our best to take it into account as we revise the domestic guidance.

Am I correct in that, Kimberly?

CHAIRMAN BYRN: Bob, on this -- the three tiered proposal, we still have these questions about the definition of intrinsically unstable and complex dosage forms. Would that be resolved by your committee, those definitions, or how do you propose to handle that?

DR. SEEVERS: As I said, we have a more than adequate set of commentary from the public at this point

to address that and knowing what the concerns are and perhaps what changes need to be made. I'm not prepared today to make a specific proposal and say this is the change that we're going to do.

We are aware of that and I think can make specific changes. It's very important that this be done properly, but that's very much at a detailed level that I don't think would be appropriate for the subcommittee to spend time on today.

MR. LACHMAN: You have some examples here, Bob, don't you, in the draft document here of the ones that are complex or could be problematic? And that's the modified release solid dosage forms, lyophilized products, liposomal formulations.

CHAIRMAN BYRN: Which one are you reading from?

DR. SEEVERS: That's in the question that we handed out today?

MR. LACHMAN: Yes.

DR. SEEVERS: Okay.

MR. LACHMAN: So that's in here as examples. If there are other ones that have to be added, that has

to be looked at. But there are examples in here.

DR. SEEVERS: There are examples in there. What we've heard from industry is if a firm is making modified release products, generally they feel modified release products don't belong in the major concern category.

If a firm is making sterile lyophilized powders, they feel that sterile lyophilized powders don't belong in the major category. And each of those examples we've received comments with specific arguments addressing whether or not it should belong in that category.

What we need to do is go through those comments, address the scientific issues that are presented there, and make a final determination. The basic idea that we tried to come up with is less based on the manufacturing process, more based on the complexity of the drug product itself, and the liability of the drug product to stability failure.

Without going into too much detail, I think we can all agree that most of the stability failures that are seen in practice relate to drug release

characteristics, dissolution, etc., and less to impurities or to potency.

That's why dosage forms that are -- where the modified release of the dose is a key characteristic of the dosage form present in our mind a greater concern.

But again, I think that for each of those dosage forms here, I can point you to specific comments in the docket where firms that are making that dosage form have said "for the following reasons, you can be less concerned about our dosage form." We need to address those.

DR. PECK: Steve.

In the comments you received, were there comments about the definitions for major, moderate and minor in terms of expansion of those notations?

DR. SEEVERS: No, there were not. Let me say that we are working with the group within the -- the stability committee is working with the group within the Agency that is revising the 31470 regulation and the 31470 guidance where these concepts are key, and we will be consistent with what comes out of that group.

So at this -- but we will be following them in time. At this point, it's premature to discuss that because that group has to do its work first.

DR. PECK: Thank you.

CHAIRMAN BYRN: One more question. How about that definition of "intrinsically unstable"; is that being addressed?

DR. SEEVERS: That will have to be addressed. I don't have a nice, neat sentence to trod out for you at this point. I think the concept that we are likely to rely on is the stability history, what's been seen in primary and supportive stability data.

CHAIRMAN BYRN: Just as a matter of sort of a side bar, the academic experts spent considerable time talking about intrinsically unstable drug substances and issues surrounding those, so that's an issue. While there aren't that many, the ones that are intrinsically unstable are problems.

Okay, so that's the first -- we've had discussion on the first proposal. And it seems, if I could summarize, that there would be minimal opposition to that as an alternative based on these discussions that

we've had.

Is there anything else anybody would like to say about that?

Okay, let's go to the second alternative which we're calling a hybrid, which is a hybrid between the original site specific proposal and the third alternative. Can we have some comment on that to determine whether there is any support for that either as an alternative or as a primary approach to the guidance?

Maybe Scott just wants to reiterate. You mentioned that that would not achieve any of the logistical goals, to use Bob's comment. That would not achieve any of the logistical goals of PhRMA, is that correct?

DR. REYNOLDS: Yes, I think it carries basically the same burden as the first, and it carries the same liability of not providing the same opportunities for the best tool as the first as well.

DR. SEEVERS: I would suggest that it actually has greater liability because, in order to develop adequate stability as a primary stability batch at the commercial site, you would have to move your time

line back a year or more.

That being said, my own personal sense is there may be cases where this would be useful. If we leave it out of a recommendation in the guidance, that would not preclude a firm from doing just what the firm who suggested this did, and that is to bring it up on their own.

What we would like to avoid is doing everything on a case by case basis, but to provide guidance that's useful to the vast majority of cases. And where a firm has an alternative that may be to their advantage in a specific case, we're always open to discussing that.

MR. BRADLEY: I would say that while the guidance should give a comfort level to the industry as to what is acceptable, it shouldn't necessarily preclude something that everyone would consider valid even though most companies would not want to use it.

So therefore, it might be easier for the Agency to outline several alternatives that would be acceptable if a company chose to use those over the primary one that's stated in the guidance. So as long as

it's not required -- I think that's been the problem is not whether something was allowed, but whether it would be required.

And if it's -- if what is being required is not reasonable or possible by the vast majority of firms, then it would be unacceptable in industry's sight. But that doesn't mean that something else that one company might prefer to use for one reason or another should be excluded.

CHAIRMAN BYRN: Are you proposing, Bill, that we -- because one alternative would be that we could remove that and not mention it at all. We could recommend that it not be mentioned in the guidance. But I think you were saying that maybe some sentences that allowed this or indicated that, you know, this is another alternative should be left in the guidance.

Is that what you're suggesting?

MR. BRADLEY: I'm not recommending one thing or another, but it would seem to me to be easier on the Agency if it were to include alternatives that then it would not have to address on an individual product basis.

DR. SEEVERS: I agree with that. My concern is that the guidance not grow unwieldy with covering every alternative that's possible. Just as Kimberly beautifully read the standard conflict of interest statement, there is a standard paragraph that's in the microscopic print in a footnote on the first page of every industry guidance.

I can't quote it exactly, but basically it says this places no obligation on the Agency or on industry. The sense of that, apart from the legalese, is that if a firm has another way of supporting what it wants to do, another data set, another way of obtaining the data, the firm is welcome to discuss that with us and we can come to an agreement that, in that particular case, a different approach is acceptable.

I would rather not, in revising the stability guidance, come up with what amounts to a Chinese restaurant menu for site specific stability to address the issue we're trying to address of sameness. Two options -- speaking just from myself and the revision process, two options are workable in terms of spelling something out in the guidance.

When we go beyond that, I think it may become unwieldy and less useful to both the Agency and to industry.

MR. BRADLEY: I agree with Bob that we wouldn't want to see an unwieldy guidance either, which is why I didn't specifically recommend that this be included.

CHAIRMAN BYRN: So maybe the most appropriate response is to leave this with the committee to determine whether -- it sounds like we have this -- if this were presented, it would be a second alternative, not a first alternative, and we can leave it with the committee to determine whether it makes it unwieldy and falls under the standard disclaimer at the start of the guidance.

Is that okay with everybody if we just leave it to the committee? Okay, so we're going to leave option two to the committee. Option one is the first alternative. Well, by process of elimination, that means option three would be the primary approach.

So let's continue our discussion of option three. As we said, the discussion was continuing along

the lines that first there's a discrepancy between the Agency's proposal of option three and PhRMA, and that discrepancy is whether a validation summary would be provided, and we were discussing the details of that.

So I think we can go back to that discussion now.

DR. SEEVERS: Let me suggest an alternative to a validation summary that would be something that I think could be readily done without getting into this gray area between the proapproval inspection and the review at the center, and that would be the following:

Right now, firms submit executed batch records typically of pilot batches. And at least one, sometimes more, are submitted with a new application and with an ANDA. Could we have the executed batch record of one of the three validation lots along with those three certificates of analysis?

That would not be qualitatively different than the executed batch record that's being submitted for the pilot data. It would provide useful information to the reviewer in that he or she would be seeing the batch record of the material produced as it is going to be

produced for commercial sale.

DR. KASUBIK: Are you proposing that as instead of or in addition to?

DR. SEEVERS: Heavens, instead of. One discussion that we've had with industry over the years is how many batch records are really necessary. And we've seen volumes and volumes of batch records. We do not need all of those. And as we complete work on the technical document, some of those issues will be resolved and they're on paper.

But my proposal would be instead of an executed batch record for a pilot batch. It seems to me on the fact of it that that would be more valuable for a reviewer because it's the actual -- right now we're seeing the proposed batch record for commercial.

Seeing one executed I think would be valuable, but I would not propose it in addition to; I would propose it as an alternative to.

DR. REYNOLDS: I want to make sure I understand. The mechanism by which you feel you see a pilot batch record is through the NDA.

DR. SEEVERS: Right now we see it in the

NDA. Typically it's either for a primary stability lot or for a clinical lot. We see at least one, sometimes more, executed batch records. What I'm suggesting is, instead of a validation summary, which, Scott, you're saying gets the review function well into the field inspector's job, something that a reviewer now sees is the executed batch record for a batch made at the pilot plant either clinical or stability.

If instead of that we saw the executed batch record for the validation lot, you would not be submitting additional information, but the information that you submit would be connected to the commercial site.

DR. REYNOLDS: Yes, I think it might be a little hard to manage the either/or aspect of that because the -- you're trading off the pilot batch record in the NDA versus the validation batch record at some point during the review process.

So that might be a difficult way to manage that. And I guess I would also ask -- we should think carefully about what benefit that really provides the reviewer. If the manufacturing process description is in

the NDA, the obligation for the firm is to validate the process using that same manufacturing process.

The confirmation of that is done as part of proapproval inspection. So I think we should ask ourselves are we really adding new value by having that there and could we really manage this either/or aspect since we're talking about information coming in by two different mechanisms.

DR. SEEVERS: Well, I think it would add value and here's why. In a significant proportion of proapproval inspections of the commercial site, no product has been made as yet when the inspector arrives because the inspection is scheduled as soon as is practical so that it can be completed and any issues that might result in a 483 can be resolved before the goal date.

That's beneficial to the Agency and to industry. What that means then is that the actual validation process data that we're saying is not a center review function but a field review function may not be seen until the next GNP inspection, which could be the following year or two years later.

That's the situation now. And that would not change under this proposal. By seeing the executed batch record instead of the one for the pilot batch, the actual validated lot production could be looked at.

Again, not as an inspector would look at it, but as a reviewer in the center would look at it.

DR. KASUBIK: If this record had to be submitted as part of making the NDA acceptable for review, then this would change the timing considerably.

DR. SEEVERS: No, no, we're not talking about submitting it at the time the NDA comes in. It would come in at the same time the certificate of analysis comes in for the validation lot. And that's a topic that we all know we need to get to is timing.

We may not want to go there just yet, but --

DR. KASUBIK: Okay.

DR. SEEVERS: -- I'm suggesting that this would come in at the same time as the certificates of analysis, which would be very much toward the end of the review process.

DR. KASUBIK: Okay.

CHAIRMAN BYRN: And you're suggesting this

would replace the need for a validation summary? So now what --

DR. SEEVERS: Right.

CHAIRMAN BYRN: Your proposal would be that the three certificate of analyses would come in along with one executed batch record from one of those certificate of analyses?

DR. SEEVERS: That's correct.

CHAIRMAN BYRN: And then no summary?

DR. SEEVERS: I think we could live with that.

DR. PECK: I'm curious as what is being defined as the summary of the validation process. What does it encompass?

DR. SEEVERS: I need to comment on that. Remember, this came from a specific firm's proposal. We have talked with that firm and, as Dr. Chen mentioned, that NDA has not yet been submitted. We have not come to a final agreement with that firm.

I think Scott's point is that that notion is somewhat amorphous and, if it were to be used, would have to be very carefully defined and limited. So your

question is a good one. It's not one that has been answered yet in our discussions with this individual firm.

And I think we would need to work further with industry in general to come to an agreement if we decide that this validation summary is an important part and adds value to the validation lot release data.

The reason I suggested the executed batch record -- and I want to give credit to Dr. Chen for the original idea -- is that that's a concrete document that already exists. It could take the place of a document that we're seeing now that industry is submitting at the time of NDA submission.

It would add value in the sense of being the actual executed batch record for the commercial site.

DR. REYNOLDS: Do you see it as value because it's an additional confirmation that yes, the validation batches were actually made; or do you see it as something that would be scrutinized and reviewed for completeness and whether it was -- provided all the possible -- I'm just trying to understand what the specific intent is to get out of that.

DR. SEEVERS: One thing it will provide is the exact equipment that's used. It will make clear any changes in the manufacturing that have been made in moving from the pilot site to the commercial site, something that is not always present in an NDA submission prior to approval.

Now, let me make a general comment here. We will, as an Agency, if we adopt something like option three, have to do a great deal of education both of the center reviewers, of the field personnel, and then an industry training on the guidance.

I spent a very productive afternoon last week with our compliance staff discussing this option in preparation for today, because they're concerned as well. What we don't want to have is center reviewers trying to perform functions that are better done by field inspectors.

You, as an industry, do not want to be in double jeopardy. So we're in complete agreement here. Now, no matter what we do, there will always be individual errors in judgement. Our commitment would be, one, to provide the appropriate education to our staff;

and two, to follow up on any problems that arise.

There is no doubt in my mind that by focusing attention at the center on the validation lots it will create some confusion. We will do our best to avoid that by education. And when problems arise, we will deal with them appropriately.

DR. KASUBIK: I presume that the same criteria would then be applied to an ANDA, that the validation record would be substituted for the current batch record that's submitted?

DR. SEEVERS: Let me speak to that. This goes back to what Leon asked me before. I think it would be appropriate to say that the current requirement of one batch three month accelerated stability data when an ANDA is submitted represents the primary stability data for the ANDA.

If we can agree on that, then that's analogous to the ICH data package for an NDA. That would not change. What would be available is if an ANDA firm wished to change its commercial production site during the review process, this validation lot release data option would be available to them.

My understanding is that that is an unusual occurrence. So I don't think that the stability data for an ANDA, in terms of its submission, would change dramatically.

DR. KASUBIK: Let me make sure I understand that then. When an ANDA would get submitted, it would get submitted as it is now --

DR. SEEVERS: Correct.

DR. KASUBIK: -- and the approval would not depend upon submitting then a validation record later on?

DR. SEEVERS: Not unless --

DR. KASUBIK: Unless they changed the site from the original.

DR. SEEVERS: Right, because generally an ANDA has that one batch made at the proposed commercial site. In those rate instances where the site has changed, this would provide a way of dealing with it.

DR. KASUBIK: Okay.

MR. LACHMAN: If the site isn't changed, normally the validation batch is made after approval. So it's --

DR. KASUBIK: Yes, that's correct.

CHAIRMAN BYRN: Okay, back on this discussion. Now we're talking about substituting the validation summary with a validation batch record on one of the three lots they had the certificate of analysis.

Are there any other thoughts that anybody would like to express at this time about that concept?

DR. REYNOLDS: I think the only comment I want to make is that we need -- from the PhRMA perspective, we view the proposal that we made actually as a significant effort towards compromise. Validation is not a requirement prior to approval.

And we're looking for as simple and streamlined a manner to provide evidence that validation has been completed, a tidy document to provide that, provide all of the additional information to support the details of validation were carried out, that the plans for validation were carried out and established in accordance with the development work that was done and the site situation.

And we're trying to do that in as simply a way, provide all that information and not provide an

opportunity for confusion to develop, as Bob mentioned, as a result of duplicate review and, you know, potential, you know, different skill sets that people look in at those data.

And I think we start to run -- this option of providing the batch record starts to get into that arena. And I would again suggest that we can get the best benefit out of establishing that the validation was completed through that certificate of analysis, and that we really don't have to go to that batch record level, and we don't beg the other issues of potential confusion or potential double jeopardy or potential duplicate review of the information.

MR. LACHMAN: Can I ask a question on this? As part of the submission of these batch records for the validation batches or the certification, or C of A for those validation batches, based on that submission, you're certifying that the validation was completed adequately?

DR. REYNOLDS: I think that could be done implicitly and it could be done explicitly. I think implicitly it's there. I think it's also possible to

develop an explicit statement to that certificate of analysis that yes, these were three validation batches, and yes, the firm is establishing that the validation was completed.

MR. LACHMAN: I would think that would be more useful than a batch record personally.

DR. SEEVERS: I proposed the batch record because it seemed like a reasonable alternative to the validation summary. I think that what I'm hearing from the committee members is the certificates of analysis ought to be able to stand by themselves without additional submissions.

MR. LACHMAN: With the certification that the validation was completed.

CHAIRMAN BYRN: When you say certification, Leon, you're talking about a --

MR. LACHMAN: It was successfully completed.

CHAIRMAN BYRN: -- a statement that would just say -- a statement would go along with these batch records.

MR. LACHMAN: With the three C of A's.

CHAIRMAN BYRN: So there would just be a

simple one sentence or two sentence certification, but it would state -- it would state that the validation had been completed successfully.

MR. LACHMAN: And then it's the field to verify it, right.

CHAIRMAN BYRN: Is that -- are there comments by the committee on that proposal?

MR. LACHMAN: I think that doesn't interfere with the field's responsibility and also probably satisfies the reviewer's concerns.

DR. SEEVERS: Can I go back, changing the topic just a little bit, to a statement that Scott made a few minutes ago, which I think is a crucial one. Two things.

One, you noted that PhRMA has moved considerably on this. And I say that we appreciate that. One concern is the concern of timing. Right now it is my understanding that a significant proportion of firms do their validation at the commercial site post approval.

How would that affect this proposal? How would that be workable?

DR. REYNOLDS: You're exactly right. And

that is -- that's the burden that the firm is going to carry with this compromise. This makes validation an assumed condition for approval now, and that's going to add burden to the firm to carry out that exercise always before approval rather than being able to manage it right around the approval time.

So we're talking about people having to routinely -- or not routinely, but every time shift that exercise to always occur shortly before approval.

DR. SEEVERS: Let me suggest how the Agency might handle this issue and then I'd be interested to hear what the committee members think. I think we could handle the availability of these certificates of analysis in a similar way that we currently handle the availability of a final report on the inspection.

Which is to say if an inspection has been done, a 483 issued, and the issues are not resolved at the time that we have to take action, we would recommend, if everything else is okay, an approvable action pending resolution of the inspection issues.

We could do the same thing saying that we would recommend an approvable action pending availability

of acceptable certificates of analysis on the validation release data.

MR. LACHMAN: That would still hold up marketing though.

DR. SEEVERS: It would indeed.

MR. LACHMAN: Okay.

MS. MALIK: If I could comment and maybe ask for some information. I would agree that having to submit process validation in the time frame that PhRMA suggested would, for some product lines, companies, part of the industry, essentially preclude them from that option because yes, they do perform either all or some of that process validation post approval.

And some of that is -- a lot of it, in fact, is related to, you know, is it a new drug entity. I mean, even many NDAs are not new drug entities today. How many similar products you're manufacturing, the complexity of the dosage form and the manufacture.

If we move towards what you just proposed in terms of the review of that information, what type of timing do you see as reasonable for the review?

DR. SEEVERS: Well, remember that it would

not hold up marketing any differently than completing validation holds up marketing now. What we would need to do, if we issue an approvable action -- let's make it very, very simple.

Based solely -- not on clinical issues or pharm tox or any other CMC issues. Based solely on the availability of those data, we would want to turn around an approval as promptly as possible when those data become available.

The result would be no significant change in the time line from the present.

DR. REYNOLDS: Yes, I think you'll hear some other comments about how this would relate to FDAMA in the presentation this afternoon. But the details of how this would be done I think are going to have to be looked at pretty carefully because, you know, FDAMA does not allow for anything but a very, very significant deficiency to CMC section to withhold approval.

So I see it being a little -- we're going to have to spend some time looking at the details of how this would be implemented because proapproval -- I mean, sorry -- validation has to be done before the product is

sent out the door.

But I'm concerned that we're going to end up --

DR. SEEVERS: You make a good point. It might be more appropriate then to put this in as a post approval commitment that those data would be provided prior to marketing. That's one option that's consistent with what you're saying.

DR. REYNOLDS: And that's basically the burden that people have right now.

DR. SEEVERS: I think the goal would be, in adopting this, to take what works in the current system and provide as minimal a change as possible.

MR. SHEININ: I think the whole gist of this alternate proposal that came in from one of the drug companies was a -- is an alternative to what we were suggesting in terms of site specific stability. And the proposal, as I remember it, was that those -- the certificates of analysis and those three batches would be submitted a minimum of three months prior to the due date.

Then there was some thought of maybe phasing

that in over a period of time because of schedules that companies have come up with in terms of their marketing plans. So over a three year period, that timing would be moved up from one month before the due date to two months to three months over that period of time to allow capital expenditures and building and things to be done.

It seems to me if we were to go to a system where this was a Phase IV commitment, then we're in the same place we are today, but we have no other data to verify that technology transfer has been done because there wouldn't be any site specific stability.

So I don't think that's a workable solution to make it a Phase IV commitment. I do think the fact that we're talking about the timing and some of the problems that the timing might create for some companies is a very strong argument on why we want to have more than one proposal in the guidance, if that's the direction we end up with.

To limit it to one, yes it's a guidance and companies can always have an alternate approach; but if we have more than one option available, then, depending on the company's marketing plans, they could choose one

over the other and I think that would be a good thing to have.

I just -- I would really be strongly against saying that would be a Phase IV commitment. The whole idea was that those data on those three batches would be available prior to the approval of the application. And I agree, we do not want to hold up approval of an application waiting for those data.

So it would have to be one approach or the other. And either way, there would have to be something done either prior to approval or depending on the three tiered approach. There's one option in there for the products where there would be a minor -- that in the minor category, that those stability data could come in post approval.

DR. REYNOLDS: Again, I think you'll see in the subsequent presentation some -- you know, the suggested kind of roll out of when that could be submitted prior to the PDUFA date. I think the question still is out there about why an approvable letter couldn't be issued and with the understanding that it was contingent upon receipt of these data.

DR. SEEVERS: I think that's what I said, an approvable letter. An approval letter with a Phase IV commitment is what Eric is saying would not work because then there would be no up front -- there would be no data before approval in the normal user fee review time.

So part of what we're hearing from PhRMA -- and, as you say, I snuck a peek at Toby's notes. What we're hearing is that part of this proposal would represent a phased in implementation in terms of the timing of the submission, but it would always be before the goal date.

And if the data are not available before the goal date -- and we recognize that schedules change, things happen -- then what I understand Eric to be saying is we would not be able to recommend, from a CMC point of view, straight approval, but rather an approvable pending submission of those data.

Now, one of the things that we need to say is right now, if you have an approvable action for CMC or anything else and you submit the data to be a complete response, there is, according to FDAMA, a certain period of time in which the Agency must then act on that

submission.

If the only thing you're submitting are those three certificates of analysis, it would be unlikely that we will take that full amount of time to respond. I don't know that we need to provide a separate commitment and schedule because I don't think this is going to happen very often that the only issue would be the availability of those data.

However, if it is, we ought to be able to respond very promptly so as not to delay marketing as soon as those data are available. In practice, however, there will be clinical questions, there will be pharm tox questions, probably there will be other CMC questions to be addressed that result in an approvable action rather than a straight approval.

MR. SHEININ: I want to clarify what I said. I think if the only thing standing between approval of an application is the data on those three certificates of analysis, I don't think we could make that an approvability issue.

And I think that's the fallacy here, that either those data have to come in prior to the due date

or we have to have the other alternative as an approach. I don't think it would be workable to hold up approval if that was the only issue.

And I agree with Bob. Most of the time there will be more issues than that. But as we move further into FDAMA too, I think the tendency is to try to resolve as many of the issues as possible prior to the initial due date so that the initial action would be an approval.

And I believe the data showed from last year that somewhere in the order of 50% of the NDAs were being approved on the first cycle. You know, I could sense that I don't think the Agency would look very favorably on holding up approval only for those certificates of analysis.

And I don't want to speak for industry, but I can almost guarantee that if it was one of your companies and the only thing standing between you and approval were those three certificates of analysis, there would be a very loud squawk that could be heard across the country.

DR. SEEVERS: All the way to Capitol Hill.

MR. SHEININ: So I don't think that's a workable solution.

DR. SEEVERS: So what you're saying, Eric, is that there has to be an absolutely firm commitment to provide those data in a timely fashion. And that's going to be a problem because not every firm is going to meet that commitment.

MR. SHEININ: That's why we have -- you would have an alternative program in the guidance and that would fall back to the three tiered proposal.

DR. SEEVERS: So we're saying do one or the other, but don't do one and then not get the data to us on time?

MR. SHEININ: That's right.

CHAIRMAN BYRN: Maybe this -- we're scheduled for a break at 10:15. Why don't we take a break right now and reassemble at 10:30. It seems that we have two open questions that we're discussing or we need to work on a little bit more, and that is the validation -- the question of the validation summary, and then we probably need to discuss this timing issue in a little bit more detail.

So let's reassemble at 10:30.

(Whereupon, the foregoing matter went off the record at 10:10 a.m. and went back on the record at 10:31 a.m.)

CHAIRMAN BYRN: We'll start in about two minutes.

Okay, we've decided to move ahead with the open public hearing. The reason for this is that these timing issues that we were discussing prior to the break are intimately related to some of the presentations in the open public hearing, so we felt it would be most appropriate to go ahead and have those issues addressed by the public, and then the committee could continue discussion.

The order of the open public hearing is Tony Amann from Eon Labs will speak first, then Toby Massa, and then we will open it up to you all. And any of you that would like to make a presentation would be welcome.

So we'll begin with Tony.

DR. AMANN: Okay, thank you, Steve.

I'm speaking on behalf of the NAPM. I am the chairman of the NAPM Technical Committee, and the

comments will result as a joint of the generic -- at least from the generic, one of the generic associations.

Next slide, please.

I think the overall principle, as we've already mentioned this morning, one thing is that NAPM is not challenging the requirement of three full validated production batches at production site.

However, because of the situation with generics and because there is really no target date set of when we have approval, basically we want to have the little caveat with our requirement be prior to marketing rather than prior to the approval.

Next slide, please.

There were some comments, at least some proposals, that came out and I'd like to make a couple of comments on those proposals. The comment one was that there' s a major requirement for modified release and transdermal patches.

And again, they require stability studies of three batches.

Next slide, please.

I think again -- and we've talked about it

previously, at least for generics, is that there should be a consideration to be given for the body of data available at the same time that a certain amount of SUPAC change are allowed, which actually can be done prior to approval as well, and some parts are already being used right now.

And the other one at the end is there's really no evidence that modified release and transdermal patches behave any different from the simple dosage forms. At least at the last advisory committee meeting, when Dr. Seevers pointed out quite a few of the failures when we reviewed those things, we pretty well felt that those failures were random event as it relates to site, but were more involved with issues that would have occurred even if they would have been done at the same site.

Next slide, please.

What the NAPM recommends, at least for the modified and transdermal, is that the stability studies on one batch would be sufficient or should be sufficient if sufficient primary data is available. Again, at the time that the project is approved, we're talking about

for transdermal patches 20, 25,000 units versus 100,000 for tablets.

And our contention is that it's probably more viable and certainly more meaningful to have full production batches of three, four hundred thousand, maybe a million patches, as well as a million or plus tablets.

And certainly if there's no body of information available, then certainly one can review again whether or not the three data or three lots is sufficient. And certainly some of these, one or maybe two of those batches, could be laboratory scale up batches.

Next slide, please.

A common one again was that the consideration of -- at least for generics again -- that the metered dose inhales in dry powder inhalers should be major changes and would require again three stability batches even prior to submission.

And next slide, please.

The comment we have here is that basically with all those, the device really controls the particle size, spray pattern, amount delivered; that the

formulation in itself or for these metered dose and dry powder inhalers is really a minimal insofar as what is being done really at the site.

Therefore, it is questionable whether or not there really needs to be three batches to be done when you have a site change rather than to have one.

Next slide, please.

The third comment really comes again. Again, I think it really is a point where it comes to about the submission of stability data. There was one proposal being made about having it midpoint in review cycle.

Well, with ANDAs, we don't really know when the midpoint is. And if sometime doing the time data review process being done, how is it going to be handled? Certainly there's no issue when you have to do it with the approval with initial submission.

Certainly there's no issue when you do it after the review cycle is completed. But during there, there's a couple of things that really is sort of concerning to us.

Next slide, please.

And that is really that when you do have a submission, with a submission, the first response from the FDA, would that -- if we do submit it with a first response or any response, are you going to go back again to the beginning.

Because, at this point, certainly any kind of stability information would be considered a major document to be submitted during a review. And in this case, in most cases, we're going to wind up being at beginning again and lose all of our sight.

That's really not acceptable from a generic point of view. We don't want to do that. Then the other case is this first response minor? Would that be considered midpoint? Doing a major, certainly you can submit things because a major amendment is going to put you back more or less then you would release anyway, so therefore submitting that takes time.

But again, it's really not an ideal situation, so we really don't recommend to have major amount of data to be submitted during a review cycle because it will kick us back again. It will affect our approval, and that's not what we're trying to do.

Last slide, please.

Really what we come down to is again that the support -- and this is really sort of in concurrence with everything I've heard this morning -- is we certainly have the same recommendation that the statement about the release data on three validation lots made at the commercial site plus a summary of the validation process, if the firm has submitted the recommended primary stability data required for ANDAs.

That certainly is not unusual because those things are being done right now. We don't want to get in double jeopardy, as Dr. Seevers pointed out this morning, that we will have this information at both the district reviews and then we have the Agency -- CDER review it as well.

That's going to cause some conflicts. But the information is there. Validation batches are being done. And we have -- the contention is that based upon everything that we're doing, we are validating the process at the manufacturing site prior to manufacturing.

And I think I want to hit the -- prior to marketing. And I want to point it out because there is

some major differences in how the submissions are being handled and NDAs and ANDAs.

Thank you.

CHAIRMAN BYRN: Are there any points of clarification for Tony, any questions, clarification questions?

DR. SEEVERS: I just want to point out that Dr. Amann's comments are reflected in the public record already, and these are exactly what I was referring to before when I said that we want to take these comments into consideration as we provide a revision of the site specific stability option for the final guidance.

The key point I just want to clarify that the generic industry is concerned about is that we had proposed that three batches would be necessary up front with accelerated stability rather than one for certain dosage forms, the ones that you outlined in your presentation, and that is your key concern.

Is that correct?

DR. AMANN: Yes, that's one of the key concerns, yes.

DR. SEEVERS: Okay. Would you agree that

the data submitted in an ANDA, currently one batch, three months accelerated for all dosage forms, serves as the primary stability data for that drug?

DR. AMANN: Yes, I would.

DR. SEEVERS: Okay.

CHAIRMAN BYRN: Any other questions?

Okay, thanks, Dr. Amann.

MR. SHEININ: I have a couple of questions. One, in your -- on your slide with the NAPM recommendation where you said stability studies on three batches, if insufficient primary data are not available would be a moderate change, you didn't mention this, but it's on your slide that, of the three batches then, two could be lab scale in your opinion and only one would have to be pilot scale.

Is that what you're saying?

DR. AMANN: Yes, one would be the regular normal one-tenth batch or 100,000 plus.

MR. SHEININ: And the other two would be lab scale --

DR. AMANN: Yes.

MR. SHEININ: -- for an ANDA?

DR. AMANN: Yes.

MR. SHEININ: Okay. And from your conclusion, what you're saying -- I want to get clear in my mind -- is that if you went with your recommendation that you would have release data on the three validation batches, from your perspective this would come in after approval?

DR. AMANN: There's two things. The answer is it could be after or before. There's two things. Approvals for ANDAs sometimes occurs a year or so prior to the market exclusivity. So we don't need to want to make the batches before then because at that time that the market exclusivity expires and we can go on the market, we basically have to throw the three batches away because we don't have enough expiration dating.

So this is why we're talking about the point prior to marketing, which is really a requirement now.

MR. SHEININ: Those are called tentative approvals, I think. Is that what they call them?

DR. AMANN: Yes.

MR. SHEININ: Okay. And if it was an approval where there is no question about -- the patent

is expiring now and you're able to market the day it's approved, how would that fall into that situation?

DR. AMANN: If we would know exactly when we would get the approval, then that would be certainly a way that we can organize it so it can be done prior. But we -- at this point, at least at our firm, we have a very difficult time anticipating when we get the final approval.

DR. SEEVERS: I have a suggestion for knowing when you get the final approval. If you agree to user fees, then --

(Laughter.)

DR. AMANN: No comment.

CHAIRMAN BYRN: Other questions for Dr. Amann?

Okay, thanks very much, Tony.

Okay, our next speaker will be Dr. Toby Massa from Eli Lilly speaking with PhRMA comments. And as I said, many of these comments will be related to the timing issues that we were discussing.

DR. MASSA: Good morning. I'm Toby Massa. I'm Director of Regulatory Affairs at Eli Lilly, and I am

chairing the working group at PhRMA on site specific stability and I'm addressing my comments today as a PhRMA rep.

PhRMA has commented numerous times in the recent past, and these are just some of the interactions we've had with FDA on the issue of site specific stability. Obviously we've been very involved and have commented quite frequently.

In the past, we've made comments to the 1987 guidance, as well as the draft guidance from '98 and the revised guidance in '99. And I'd like to review some of the comments that we've made. And some of these are kind of rehash from the March 31st meeting, but I think it's important for the committee to hear them again.

In the 1987 guidance, there is no explicit requirement for site specific stability for the drug substance. As a matter of fact, that guidance says that the stability of the drug substance is to be demonstrated once per method of manufacture. And there is nothing in there that refers to site changes or scale up.

Bob and I have debated quite a lot on the second issue as to whether or not there is a product

requirement. And even if we concede on the fact that there is a product requirement, we feel that that's superseded by ICH Q1A which FDA signed and published in 1994.

And that brings us to comments on the '98 document. We definitely do feel that the ICH document does make a statement regarding site of manufacture. The issue and debate revolves around the comment on pilot scale versus pilot site.

But clearly the ICH document does say that the batches should be representative of commercial, they can be made at pilot scale. We've always interpreted that meaning pilot site. But it also goes on to say that if production batches are not included in the initial application, that the applicant is to make a commitment to put the first production batches into the commercial stability program.

And in the ICH Q1 revisions, there is a definition being proposed of what a production batch is. And a production batch specifically is being defined as made at the commercial site with commercial equipment at commercial scale.

I think I have that right. Now, to our way of thinking, it may be intuitive, but why would ICH have those comments in there if they did not feel site specific stability was not a requirement? Also in the '98 draft we kept asking for what is the question we're trying to answer with site specific stability.

It did not become clear to us until the March 31st meeting when FDA presented their example of issues that they felt were related to site stability issues or site stability factors. And a group of us in industry looked at these and we felt that in nine out of the ten cases, and maybe ten out of the ten cases, that these issues are really more related to validation and qualification rather than stability.

Next one, please.

Based on that and some discussions that have been held since the March 31st meeting, we've put together a compromised position, and a lot of this has been discussed earlier, and that consists of certificates of analysis for the three validation lots, submission to the NDA three months prior to the PDUFA action letter date with the three year phase in, and that addresses

some of the issues that were mentioned before about some companies not doing validation as part of the proapproval requirement.

And we felt that this would be an adequate way of getting those companies adequate time to modify their plans to come up to the three month submission date. The validation batches, since more than likely they are going to end up being the first three commercial lots, would go up onto a stability program, and those data would be submitted in the annual report as per current practice.

We do not feel that validation date, nor summaries of the validation, should be submitted. Now, our compromise we feel better addresses FDA concerns because it addresses the issue of validation and has the process been properly transferred.

And we've talked a lot about that this morning already. I think the issue of should validation data or summaries be submitted is addressed by the second bullet. We have a system in place right now in which the field addresses GMP issues and validation issues.

And this is consistent with the 1994 letter

that Janet Woodcock and Ron Chesemore sent to industry sponsors in which the responsibilities between the field and the center were delineated.

And with regard to validation, with the exception of sterile process validation, which is the responsibility of the microbiology group at the center, all validation issues were assigned to the field.

And there's a logical reason, as Scott mentioned, for that. And that validation is not just looking at the three validation lots. It's looking at the continuum of development through scale up and validation at the site.

So we feel very strongly that that's the place where validation ought to be looked at, including validation summaries, because that's where the primary responsibility lies. If we do that, we avoid any potential for disagreements between the center and the field on interpretation of validation data, adequacy of validation.

The field are the ones who are charged to do that, and we think it ought to stay that way. And we do feel that this does represent a true compromise.

One of the things that we were asked to do in preparation for this meeting is address the issue of sameness. And I think what we're proposing is consistent with something else that was in FDAMA, Section 116, which dealt with manufacturing changes.

What we're talking about here is a site change. It may or may not be associated with scale up. Most times it is. But basically what we're talking about here is a manufacturing change. In Section 116, FDA said that a major change -- or a change would not be considered a major change if there were no changes to specs or formulation.

It also said that any manufacturing change had to be done in a GMP environment and that the process, whatever it was, had to be validated. So we think that if that's good enough for demonstrating sameness with manufacturing changes, it ought to apply here in going from a pilot plant to the commercial site.

Also, as we've discussed numerous times, this relies on validation as the indicator of process transfer. I think it really needs to be driven home that this really is a compromise for industry. For those of

you who may not be familiar with FDAMA Section 124 or the Senate report that accompanies it, these are comments that come from the Senate report.

And I think it's important to look at what that says, that the FDA can review and approve new drugs and biologics on the basis of pilot and small scale manufacturing information; that the company can be permitted to scale up to a large facility after the product is approved; and it is not the intention that the pilot plant is what's approved here.

Scale up can be done on the basis of process validation. And the key thing is that only in very rare cases should this information be required as a condition of approval. Now, in the interest of compromise, because we know that the issue of site specific stability has been a very contentious issue, we are foregoing this.

De facto, validation is going to be a condition of approval. So this truly is a large step for certainly PhRMA to take because we fought very hard to get this into FDAMA. So we really do feel that this represents true compromise.

We also feel that by virtue of the fact that

these batches will go on to stability, that FDA will get to see site specific stability, albeit it will be part of the annual report. FDA also gets to see that validation is completed and now what will be in all cases prior to approval.

Now, there's one thing I want to make sure that everybody understands what we're talking about when we talk about -- you can turn the slides off. Thank you.

We keep talking about three validation batches and three certificates of analysis. And now we're talking about possibly submitting one batch record from that validation. The reality is we're talking many batches here.

Because in most cases, you're talking multiple dose strengths, multiple package presentations. In some cases, you're talking about multiple sites. So I want to emphasize this primarily to the FDA representatives because what you're asking for is to get this data -- now we're talking about a phase in over time.

The certificates of analysis and

certification that the validation is completed we think is something that can be reviewed very quickly and should not impact on issuing of the ultimate letter in concert with the PDUFA action letter date.

While we're not necessarily opposed to submitting a batch record, because a batch record is part of the NDA whether or not it's submitted, we don't have a problem with that. The concern I would have is the review of those batch records and is that going to be done in a timely fashion that will allow any issues to be discussed and hashed out before the action letter date.

And obviously it takes time for an action letter to circulate through the Agency for signatures, so we really don't have three months. In reality, we probably only have a month and a half or two months in order for that process to occur.

So if we're talking multiple batch records here, we need to make sure that that's what we really want to do, and what's the value-added of that going to be when validation batches will be looked at or can be looked at by the field.

That's some of my comments and I'd be happy

to answer questions.

CHAIRMAN BYRN: Questions for Toby?

MR. SHEININ: I have more -- just some basic comments and questions. I think Toby is correct in saying PhRMA is coming a long way from your previous position and this does represent a true compromise.

I think the same thing can be said about the FDA position. And I hope everybody recognizes that also, that we are coming a long way from our previous position and trying to compromise to get to a point that both the regulators and the industry will be comfortable with what we have and FDA will still be fulfilling our mission of protecting the public health.

I don't want to debate some of the things you said, Toby. You know I don't agree with everything you said and you don't agree with everything that we've said, and I don't think this is the place to do that since we're moving towards compromise.

I did want to bring up one thing though, that I think at some point we may have to have a group that will try to standardize on what should be in a certificate of analysis. Those of you who worked for one

company your whole career, you probably see one type of certificate of analysis.

If you change companies or if you ever have the opportunity to work for the Agency, you see certificates of analysis that range all over the board. Some give a lot of information, some give almost no information.

And one of the areas that we would like to see in the certificate of analysis is actual numerical values. So, for example, if you're testing for the presence of an impurity or several impurities and your acceptance criteria say less than .2% of this impurity or less than 1% of total impurities, we would like to see in a certificate of analysis actual values for those impurities and not just have the COA say pass.

And I think that's something that we need to get across to all the industry, that the certificate of analysis has to have some value if it's going to supersede our desire to see the site specific stability data.

DR. MASSA: One comment I do want to make, Eric. And it's true we don't always agree, but I think

if we look at how this process has gone where there has been open dialogue and a good exchange of information, and if we also look at the BACPAC 1 process, we think those are really two good examples of how all guidance ought to be handled where there is open dialogue rather than trying to, you know, get a guidance out there by a certain time for whatever reason.

And I think it's important that we have these discussions before we get to even the draft guidance being out there, that there be -- as in the case of BACPAC. Because I think it does result in a better process and certainly a better guidance that, while we may not be totally in agreement on the guidance, it does get industry and FDA a lot closer to where we end up.

DR. SEEVERS: I'd like to comment, Toby, on your point, which I think is a very important one, that we have this magic number of three C of A's in our mind. But in reality, there will be many different packaging presentations, different strengths, etc.

I think that what would need to be done is, during the pre-NDA meeting, we would have to come to an agreement with the firm on which dosage form -- which

packaging presentations, which strengths and so forth would need to have the actual C of A's submitted --

DR. MASSA: Yeah, we'd agree with that.

DR. SEEVERS: -- rather than come to the end and have a reviewer say, "But what about the HTPE bottle intermediate size?"

DR. MASSA: Yes, we'd agree with that. That ought to be a discussion we have at end of Phase II when we talk about what the plans are to get to the actual NDA. I think that's something that absolutely ought to be included there.

I think that's the right place for it.

DR. SEEVERS: But I think that the sort of bracketing principles that we've proposed in the draft guidance may have applicability here.

DR. MASSA: Yes, we wouldn't argue with that.

CHAIRMAN BYRN: Any other questions?

Okay, thanks very much, Toby.

DR. MASSA: Thank you.

CHAIRMAN BYRN: Okay, are there comments from the floor? Would anybody like to make a comment

from the floor?

Bob Juerssi.

Bob, if you'd just come to one of the microphones. Here's one on this side and also on this side.

DR. JUERSSI: I'd like to point out that the requirement, if it goes into effect of three validation batch -- the validation being done before approval, is going to have a rather large impact in the generic area even though it's only limited to where a firm manufactures the commercial batches at a different site than the bio or test batch.

And that's because there's a lot of virtual companies in the generic business. Not every generic company manufactures or has a manufacturing facility. So they may have a bio batch made here and a commercial product made here for several reasons.

This outfit may not be able to make the size batch that's needed commercially, etc. Now, this is going to have an impact on exclusivity because it's going to affect the date of approval. And that's big. The Agency just went to a lot of trouble to talk about some

of the excesses that occur with exclusivity.

Okay, they've put out a notice, a *Federal Register* notice, that it's open for comment yet. So I think that's something this group has to consider, the impact this is going to have on the generic industry, because most generic validation is done after approval.

Some is done before. It depends on how long you have to wait for approval.

The other thing I'd like to point out or I'd like to mention, that I think I heard the following this morning: that if you took the option of sending in the three C of A's but didn't make it in in time, say three months before the PDUFA date, or you didn't make it in at all, it would not hold up approval.

I thought that's what I heard Eric Sheinin say. If that's true, who would take the other option?

MR. SHEININ: That's a very good point, Bob. And I guess partly what we would be relying on is a commitment made by a firm, and we would expect that firm to live up to that commitment. And what you're proposing is that a firm would make a commitment and then not honor it.

And that does happen. I would hate to think that that would be the norm for the pharmaceutical industry. There are perhaps other things that could be used to try to help a company meet their commitments such as what would your expiration dating period be if you didn't meet the commitment as opposed to if you did meet it.

I don't know. We would have to discuss internally, I think, some other options that we might have. But my feeling is the pharmaceutical industry is an ethical industry. And if a company makes a commitment, I would expect them to live up to it.

And as I said, I hate to think of where we're going if companies knowingly say we're going to do this and have no intention of doing it. I think we would take the pharmaceutical industry back probably 200 years.

And I hope that's not what you're suggesting will happen.

DR. JUERSSI: We would only take them back 11 or 12 years to the generic drug scandal, Eric, okay? We don't have to go back 200 years.

Hey, the other point is that some companies

may make an honest commitment to meet this, but not meet it. Maybe they can't make it by that time.

DR. SEEVERS: Let me suggest that what we would have to do is look for a pattern of abuses. If a certain firm makes a commitment and, because of circumstances beyond their control, can't meet it one time, that can be dealt with as an individual case.

If the same firm makes a commitment and repeatedly does not honor its commitments, that, I think, would be a different situation and would have to be dealt with appropriately.

CHAIRMAN BYRN: Okay, any other questions? Any other comments from the floor?

Colin.

MR. GARDNER: Colin Gardner from Merck. I think I can give a little bit of perspective on this, Bob, give some historical perspective earlier in sort of Toby and his presentation.

But this really takes us back about three years when we first learned of the FDA's belief that we have to provide site stability and we felt we were the only lone voice out there talking to the Agency about

site stability.

So I really want to commend everyone who has worked on the industry side. Not only the PhRMA side, but also the other trade organizations on the FDA on really coming to grips with this whole issue and looking at it in a scientifically sound manner, which I think has been the right way to go.

It's taken us three years to get there, but I really think we're very close to achieving something that is workable and I want to thank everybody involved.

I would just encourage my colleagues in industry to recognize that the FDA has, in fact, made significant compromise, as well as PhRMA making significant compromise, and that we are so close now that we shouldn't try to throw up a number of hurdles into the way of achieving the recognition of what I think is a sound way to move forward here.

Just a very brief comment on what Toby mentioned about the validation batches. He said there might be multiple strengths and multiple packages. The package doesn't really enter into this because these are initial release data.

So regardless of the package you're going to put it into, it's the release data. So really only it's the multiple strengths that we have to address with respect to the C of A's.

The question has been asked about whether or not the C of A is sufficient for the FDA to really recognize that we've done the validation batches, and I think Scott spoke to that in the sense that we can include a statement that the validation batches have, in fact, been completed and these are the data representing those batches.

If we really feel that we have to go beyond that and have some additional information provided to the Agency, I think I'd prefer to go with the summary of the validation batches rather than the individual batch record, and I think Pat's going to speak to this in a moment.

But I think the individual batch record speaks to one particular batch. And as Toby also indicated, although you make three validation batches, you have, if you're going to launch in a timely way, you have made probably 20 or 30 batches by the time you're

ready to launch.

So there would be many, many batch records available. All of those batch records will, of course, have minor deviations between them because there's a range for all the parameters to be made. So submitting one batch record I think does put us in double jeopardy in terms of saying this is what would be looked at historically as the perfect batch when, in fact, it's just one of many batches.

Whereas, putting -- submitting something of a summary which would indicate the critical process parameters and the critical quality attributes with the range of acceptability as a summary of how the validation batch was constructed and relating that back, as Scott indicated, to the entire development cycle is a continuum starting off from the early stages coming up through the bio batch where you actually set many of these parameters and then subsequently to the validation batches.

There is that historical perspective to put in place. And looking at those quality attributes and control parameters, I think -- and their range would be one appropriate way in providing one single batch record

to the Agency.

So again, I just want to thank everybody who's been involved in this process and I hope that we can come to an agreement today so that we can all move forward.

Thank you.

CHAIRMAN BYRN: Any questions for Colin?

MS. TWAY: I'm Pat Tway, also from Merck. And just to elaborate a little bit more, because I agree with everything that Colin has said, and I certainly do appreciate that this is huge compromises that have been made on all sides.

And I will acknowledge that our NDA is one of the two NDAs that was used as an example that has not yet been filed, but we've reached agreement on how we are going to file it and we did commit to file the C of As and a validation summary.

That was the commitment we made. And certainly we will live up to that commitment if, you know, that's where we end up and that's what people want us to do. And I honestly believe that -- while we need to work out exactly what information the center might

like to see, and I recognize double jeopardy and the rest of it as well, I think providing some form where we potentially give the critical quality attributes, we give the in process test, we give the results.

It would be easier for the reviewer to look at. We could formulate it and tabulate it and work with the center prior to filing this obviously -- than a batch record. Batch records are tremendously large. Unless you are very familiar with this batch record, you're not going to have a clue where to look for information.

And to provide one batch record, which we do now provide -- we recognize the market container batch records. But since we have never once received a single question on any of those batch records, I have to believe they sit in the back and they don't get reviewed very actively.

So while we could certainly live with providing a batch record, I think a summary in some form, which I recognize is at this point a morphous, as someone described it, but we certainly, as a company, would commit to work with the Agency for the one NDA that we've already committed for and to try it as a trial.

The NDA is to be filed in the year 2000, so we could work on that as a step forward if we wanted to. But the batch record, to me, is going to be very hard for the center to get much useful information out of, particularly when it comes in near the end of the review cycle.

CHAIRMAN BYRN: Any questions?

MR. BRENNAN: Sean Brennan, Parke Davis, Division of Warner Lambert.

I certainly also acknowledge that a lot of compromises have been made with industry and FDA, and FDA's come a long way. Just a comment back to my colleagues in industry.

I think we have to be very careful in talking about summaries of the validation process because a lot of things go on in validating the process that aren't application commitments. And if we start to open up that data or a lot of those observations again to FDA scrutiny, I think we're back into the double jeopardy situation.

So I'd just like to make that observation. And one more observation regarding certificate of

analysis. Many of us have laboratory systems that print out C of A's, having completed all the tests. And I think we should talk about a summary of the results as opposed to the actual C of A's, and I'm sure that's what you're looking for as opposed to the actual C of A used by a facility.

So it would be a summary of the results versus the performance criteria for that batch is really what you're looking for in terms of the validation batch. And I think we should maybe remove the term C of A from the guidance and focus on the actual results.

CHAIRMAN BYRN: Questions, comments?

Yes.

DR. ROY: Suva Roy, GalxoWellcome. I'd like to support the PhRMA position of providing the C of A's and no summary of the validation data. The validation data should reside where it resides, that's with the field.

Batch manufacturing record is a very useful tool as a reviewer. People over here know I used to be at FDA. I found it a very useful took to refer an application because I could see, step by step, what was

done.

And if one batch summary of the validation batches is provided, I think that does the job.

Thank you.

CHAIRMAN BYRN: Any other comments?

Yes.

DR. CHEN: Since Bob mentioned my name -- Chi Wan Chen, FDA. Since Bob mentioned my name earlier as the one behind the suggestion of one executed batch record, I'd like to explain why I had that suggestion.

I thought that would serve two purposes. And again, it's in the spirit of compromise. I think it's a good alternative to this validation summary, and it's also -- it will serve the purpose -- it will fulfill the requirement under the regulation that one executed batch record be submitted.

And in addition to this, I have another comment. A suggestion was made earlier that a certification be provided to state that the validation or technology transfer has been successfully made. I would suggest that, for the reviewer and also part of the NDA, it will be useful to also know, in addition to a

successful validation, what changes, if any, have been made to the in process controls.

I think that would be very useful. And obviously those changes have been qualified and justified, otherwise you would not have made those changes. But it would be useful for the reviewer and it would be -- I think it's not too much to ask because it should be part of the record in the NDA.

CHAIRMAN BYRN: Questions, comments, any other?

MR. LACHMAN: I think that puts you back to the validation summary if you're going to ask for that.

DR. CHEN: Probably on a smaller scale. We are not getting into discussion about operation parameters. On the other hand, in process controls is part of the NDA and is part of the center responsibility.

CHAIRMAN BYRN: Any other questions or comments?

DR. REYNOLDS: Yes, I just wanted to clarify. You're talking about in process controls which are specified in the NDA, correct? Yes.

CHAIRMAN BYRN: Okay, then we'll go to the

next section, which is continuation now by the committee to discuss approaches. Remember, we had two issues on the table. One is one we've just been discussing which relates to validation summaries.

And the second issue is the timing. Is there any feeling on the committee which one we want to take up first? I believe these are the two remaining issues to address prior to seeing if we've achieved a compromise or not.

Yes, Bob.

DR. SEEVERS: I'd like to do two things. One, I'd like to talk about the timing first. And two, I'd like to put on a mental blackboard two words that have not been spoken yet but need to be before we finish today, and those words are drug substance. We need to address how these concepts would apply to APIs.

Insofar as timing is concerned, the proposal that Toby Massa made on behalf of PhRMA of a phase in I think is reasonable and could be made workable. The amount of review actually involved in looking at the release data -- well, let's call it certificates of analysis even if it's not exactly a certificate of

analysis, but those data -- it is not great and could be accomplished fairly quickly.

Recognize, however, that as a result of seeing those data, some review issues may arise. An example would be a case where you have a drug product that is a modified release product whose pilot data suggests that the release characteristics of that drug are at one end of a specification range.

When we would review data from the commercial site that show that the release characteristics of that drug are toward the other end of the specification range, that would raise a concern that would need to be addressed.

Hopefully, the firm would note that and address it in the submission. But if not, those questions would be raised with the firm. A typical response might be a request for a post approval commitment to report stability data on that -- anything that goes out of range right away rather than just using the field alert report system.

I raise this as an issue because it's bound to come up at some point or another. It's one thing to

say that the review is simple and straightforward. What we have to recognize is that some review issues may arise as a result of seeing these data that are legitimate review issues, not a case where the center is stepping into the area where the field properly works.

MR. LACHMAN: That could be resolved by bioequivalence data to show that the extremes -- you still have them in bioequivalence.

DR. SEEVERS: Yes, but if the primary stability data show that over time the release characteristics of the modified release drug product shift toward one end of the -- from one end of a specification to the other, if you're starting out at the high end now, at the commercial site, that does raise a concern.

MR. LACHMAN: But if you did your bioequivalence at the high and low ends, --

DR. SEEVERS: As long as it stays in spec, you're okay.

MR. LACHMAN: That's right.

DR. REYNOLDS: Yes, I agree with you, that's something that would be looked at real critically.

I think the key thing is that it would have -- you know, it gets back to being able to defend the rationale for both the release data for those -- I mean the initial data for those release rates and being able to defend -- understand the stability performance of that over time.

And so I think that that would be the responsibility of the firm to show that the information in their NDA supports that release profile at release of the product.

DR. SEEVERS: And I think the firm should be willing to pay -- to commit to pay extra attention to that over time. If the issue is there at -- around the time of approval, it would be legitimate to ask the firm to submit, say, the accelerated data from those validation lots as it develops so that they could be discussed rather than waiting for an annual report.

I don't think that would be a huge burden. I don't want to go off on this sidetrack too far. I just wanted to make a point that there can be review issues with these data.

DR. REYNOLDS: I think Toby's slides also indicated that those validation lots would be lots put up

on stability as well so that the -- you know, the road's paved to do that.

CHAIRMAN BYRN: Okay, are there any other discussion of the timing issue? It sounds like the PhRMA issue at least gives a good starting point for the committee in writing the guidance.

Okay, let's go back to the validation summary -- oh, excuse me.

MS. MALIK: With respect to the timing -- and again, I'm speaking on the part of HIMA. You know, we talked earlier in terms of what is the timing for many of the companies with respect to process validation if you're not talking basically a new drug entity.

And although I think a phased in would certainly make that more palatable, I think some of the earlier discussions we had in terms of the timing of the submission of those certificates and the commitments or certifications that the company make are more appropriate to many other companies for the types of products that we do make.

DR. SEEVERS: Could you be more specific as to what you feel would work for the HIMA firms?

MS. MALIK: Well, I think the two proposals that I heard were one was -- I think, Bob, you brought up in terms of an approvable letter and we would submit that information. The other discussion that we were having was related to a post approval commitment as we make post approval commitments to do those commercial batch stability studies.

And I would agree entirely with the comments that, you know, Eric made earlier too that there is, I think, an ethical standard within the industry that we make those commitments and the expectation is that we will deliver on those commitments, and that if not, then, you know, that needs to be seriously looked at as well.

DR. SEEVERS: Okay, but I want to make sure I'm understanding you correctly that HIMA is saying that it would be difficult to meet the commitment to provide validation data before approval.

MS. MALIK: I think in the time frame that we're discussing here, it would certainly be more difficult and some of the products are fairly short dated products. So would they elect to take this route? I don't know that we would.

DR. SEEVERS: But if you had the option of doing site specific stability along the lines of the March draft proposal, you might elect to go that way?

MS. MALIK: Yes, and I think that's what makes the proposal that was stated earlier of leaving that in as a viable alternative. I think it becomes critical to those companies then.

DR. SEEVERS: Okay, one comment about that. One of the things that we have said and everybody's nodded their heads very well, but practice has shown this is not the case, is that the ICH data package is a necessary assumption for any of these.

We agreed on that back in the early 90's. We had a gentleman's agreement that we would not start enforcing it until January of 1998. We're still getting NDAs with six month's worth of data in them. Half or more of the NDAs we receive do not have the full ICH data package.

That's a very real concern when it comes to implementing any of these proposals. And what I would like to say is that we're going to have to have a third alternative for firms who do not submit the full ICH data

package in their initial submission.

More data is going to be needed in some way, shape or form from the commercial site to support that site.

MS. MALIK: Could I just ask for clarification because your comment was interesting in the number of data packages you received that don't meet those requirements. I presume from your comment that these are not cases where there has been discussion with the Agency up front.

For example, maybe it is an NDA, but it is not really a new drug entity and there has been discussions with the Agency before submission.

DR. SEEVERS: It's both. The most common question referred to me as the chair of the stability technical committee can be boiled down to the following: How short an amount of data, how short a time, how few data can we submit at the time of initial submission, and under what schedule can we let it dribble in?

That practice is absolutely antithetical to what we're trying to do here today. And what I'm saying is, in those cases we're going to need to have a third

option of additional data from the commercial site to support that site in the absence of sufficient primary stability data.

CHAIRMAN BYRN: Okay, anymore comments on timing? We'll go -- the chair will allow comments from the floor.

MR. GARDNER: Bob, just to that point, I mean I assume that if people are not living up to the regulations which were established as of the first of January 1998, that you have the right to reject the file and just refusal to file. I don't see why you don't apply that.

I'd rather do that than have us build yet another contingency into all of this that there needs to be more site stability data rather than just live up to the regulations which everybody agreed to.

DR. SEEVERS: And I would like to do that, too, except the word regulation doesn't apply. It's a guidance. And as such, we are not able to make it a requirement. I am unaware of a case where we've refused to file a new drug application because of an incomplete ICH data package.

I assure you, if you submit an NDA without stability data, we'll refuse to file it. But people are submitting it with just enough data to get by at the time of filing and then submitting it and making sure that they don't wait to submit the last little bit of data in the last three months of the review cycle where it could be considered a major amendment and extend the review clock.

I just want to get this on the table because it is an issue right now and it does affect our discussion in that we've agreed -- everybody nods their heads -- that the ICH data package represents a definition of sufficient primary stability data.

CHAIRMAN BYRN: One more comment from the floor.

Toby.

DR. MASSA: We've had a lot of discussion about this at the PhRMA stability committee, and I think we have to have a very rationale approach here. We agree that in most circumstances, yes, the ICH stability package ought to be the baseline.

And quite frankly, I agree with Colin. If

people do not have an ICH stability package, it ought to be refused to file unless you have a drug in which -- you know, if you've got the cure for cancer and you're trying to get this thing out there and the only thing that's standing in the way is some stability data, okay then you have a -- that ought to be the exception rather than the rule.

I mean, industry agreed to the ICH conditions the same way that FDA did. And you know, the whole purpose of that was to have a uniform standard. In Europe, they won't even allow a discussion of coming in with less than ICH data.

CHAIRMAN BYRN: One more comment from the -- Eric, and then we'll have a comment from the floor.

MR. SHEININ: I totally agree with you. I wish we could refuse to file those applications. The Europeans have a whole different approach. They don't consider the ICH guideline is just a guidance, it's not binding. It's considered binding, I believe. And because of our good guidance practice regulations, we cannot do that.

DR. POLLOCK: Bob Pollock, Lachman

Consultant Services.

Eric, I would respectfully disagree just based on the fact that the regulations do require an adequate stability data to be submitted with the application. In generics, if you come in with less than three months accelerated, you will receive a refuse to file letter.

I signed a lot of them. People are signing a lot of them today. I don't see why new drugs can't do the same thing.

DR. SEEVERS: We're working on it.

CHAIRMAN BYRN: Okay, anymore comments on timing? I think we've had a very good discussion and I'm sure Bob has a good picture of writing -- his committee has a good picture of writing the guidance or rewriting the guidance.

Okay, let's go back to -- we have two issues left. We need to discuss drug substance and we need to discuss the validation summary data, the whole issue around batch records.

My understanding of where this issue is, is that Leon suggested a compromise, which is what he called

a certification statement, that no validation summaries would be submitted, simply the validation batch records plus a certification that a validation had been completed properly.

I don't know whether you want to --

MR. LACHMAN: Well, it wasn't the batch records. It was the C of A.

CHAIRMAN BYRN: Right, pardon me.

MR. LACHMAN: Yes.

CHAIRMAN BYRN: Three C of A's and a certification.

MR. LACHMAN: And you know, Sean Brennan from Parke Davis made an interesting suggestion there that should they be the normal C of A's or should they be C of A's indicating that each batch met the acceptance criteria of the validation.

You know, I think it's a good point. The normal C of A's have a lot of information, but may not be pertinent to the acceptance criteria or the validation, that batch meeting the validation criteria.

DR. SEEVERS: I think we're looking for data to show that the release characteristics of the

validation lots meet the proposed specifications.

I would like to add to that. I think that Dr. Chen's suggestion that any changes to the in process controls that are submitted in the NDA should be noted at this time. They might normally be noted in a follow up annual report.

I think this is a timely place to take note of them. I think we could live with that and the certification in lieu of a summary.

CHAIRMAN BYRN: So what's being proposed here is that, in lieu of a summary, we would have a certification and we would have a notification of any deviations from in process controls.

DR. SEEVERS: Or any changes to the --

CHAIRMAN BYRN: Any changes to --

DR. SEEVERS: -- in process controls.

CHAIRMAN BYRN: Okay.

DR. REYNOLDS: I think it's changes to in process controls that are filed in the NDA.

DR. SEEVERS: Yes, exactly.

CHAIRMAN BYRN: Is there any comment on that concept?

Clarification from the floor. Identify yourself.

MR. CLARK: Bob Clark from Novardis.

Regarding in process controls, does that pertain to a drug product only or drug substance and drug product?

DR. SEEVERS: I would say both, but we really haven't discussed how these ideas would apply to drug substance. That's next on the list.

MR. CLARK: Right.

CHAIRMAN BYRN: Any other comments on this compromise, this concept?

Toby.

DR. MASSA: I just want to make sure that we understand exactly what's on the table here. Are we saying certificates of analysis or some piece of that release data and certification that the validation was successfully completed?

The third part that I'm hearing is any changes to in process controls.

DR. SEEVERS: Any changes to what I would call regulatory in process controls.

DR. MASSA: Right, in process controls submitted to the NDA.

DR. SEEVERS: Correct.

DR. MASSA: No validation summaries, and we had talked before of batch record in lieu of. We're saying that's off the table as well?

DR. SEEVERS: Right.

DR. MASSA: Just want to make sure we understand what it is we're agreeing to here.

DR. SEEVERS: What I'm saying is I think as an Agency we would live with that. I think that the batch record would provide useful information. The down side is it would require a fair amount of review time, which might be hard to come by at that point in the review cycle.

And I am not hearing a consistent agreement from the various industry reps that that would be a good thing to do or even possible to do that that point. So I think we could live without that if we have the three things we agreed on.

DR. MASSA: All right, so it's C of A data or the C of A, whatever we agree to is the proper data

set, certification that the validation is successfully completed, and any changes to NDA submitted in process controls --

DR. SEEVERS: Correct.

DR. MASSA: -- applying to presumably, depending on how the drug substance discussion goes, applying to drug substance and drug product?

DR. SEEVERS: Correct.

DR. MASSA: Okay, thank you.

MR. LACHMAN: That can be part of the certification document. Any change in in process controls could be covered there.

CHAIRMAN BYRN: Okay, any other comments? Okay, I think we've got timing and I think we've got this second issue resolved. Now we need to -- I think then the last thing we need to discuss is -- and some people were hoping to get done by noon, but we can go a few minutes longer if necessary -- is the APIs and how this applies to APIs.

Who would like to initiate that discussion?

Do you want to start, Scott?

DR. REYNOLDS: Yes, I can start very simply. I think the PhRMA position is this would apply to drug substance and drug product.

DR. SEEVERS: And from an Agency perspective, we had, in the three tiered proposal, recommendation of site specific stability data that would be necessary for a drug substance.

And in the majority of cases there, what would be needed is the standard stability commitment after a firm has demonstrated that the physical and chemical characteristics have not changed.

In cases where you're dealing with environmentally sensitive substances or substances that are known to have polymorph problems, more attention to it would be needed in terms of stability data and we spelled that out in Table 2 of our original proposal.

I think we could keep that as the alternative.

CHAIRMAN BYRN: So are we hearing the proposal that everything that we've discussed, including the two alternatives, all would apply to both drug product and drug substance?

Okay, do people just want to take a moment and see if there are any concerns -- any other issues that people want to raise?

Yes, Colin.

MR. GARDNER: Colin Gardner.

Bob, just a point of clarification. I mean, we are then saying that the batches of drug product that are validated use the drug substance that has also been validated, so I just want to clarify that that's on the table and that, in fact, it's not drug substance from somewhere else, it is the validated, final manufacturing site of drug substance that's used to produce the final manufacturing site of drug product.

DR. SEEVERS: No, the Agency has never had a policy, that I'm aware of, and I know several people will correct me if I'm wrong, that you are absolutely required to track site specific stability for each batch and each site of drug substance and to each batch and each site of drug product.

That is unworkable. What our policy has been is -- and the science underlying this. If the physical/chemical characteristics of a drug substance are

the same from two sites, the drug product stability should not be affected by different manufacturing sites of the drug substance.

What we have said in the draft guidance I think still holds. To the extent possible, you improve your data by using -- if you have more than one site of drug substance manufacture -- by using batches from different sites in your drug product stability batches.

But we said to the extent possible.

MR. GARDNER: But just to clarify, regardless of whether there's one or multiple sites of drug substance, nevertheless, the drug product made at the final manufacturing site and the data generated from those validation batches will have used drug substance from one of the final manufacturing sites for the drug substance.

Is that -- that's not what you -- that's what we believed you were saying, but you're not saying that to me?

DR. MASSA: I think what we're hearing -- correct me if I'm wrong, but I think what we're hearing is if you show that the physical/chemical characteristics

of the drug substance made at the pilot plant versus the commercial site are the same, you do not have to use validated drug substance from the commercial site to make validated drug product at its commercial site.

DR. SEEVERS: That is correct.

MR. GARDNER: Okay.

DR. SEEVERS: Otherwise your time lines would be extended by two or three years without providing additional scientific -- without providing additional scientific benefit.

CHAIRMAN BYRN: But we are saying that all of these site specific stability agreements that we've made today apply to three C of A's from drug substance manufacture, verification that validation has been completed, and any changes to in process -- regulatory in process controls, all that applies to drug substance?

DR. SEEVERS: That is correct. Now, if it happens that you have drug substance available from your intended commercial site when you're getting ready to manufacture the validation lots at the commercial site for the drug product, obviously it would be better and strengthen your case to use those.

My understanding is that, in practice, you often do not have that available because a commercial site for the drug substance may come on line late in the process.

Just one other note. This is consistent with the approach that the Agency is trying to take in the BACPACs.

CHAIRMAN BYRN: Okay, are there any other comments?

DR. KASUBIK: Could I just go back and revisit a point on the ANDAs for my own clarification? We've talked about what we would do in terms of approval of an ANDA. When we get -- let's say on a post approval situation, because this came up --

DR. SEEVERS: I'm so glad you said those words.

DR. KASUBIK: On a post approval situation, do I understand then that if a firm has an ANDA and it gets approved, and now they want to go from one site to another, they can do this by submitting three certificates of analysis and a validation?

DR. SEEVERS: I think what you're doing is

the equivalent of extending your expiration date based on accelerated data. You're extrapolating. This was the other item that I think we needed to have on our agenda. Let's say explicitly what effect do the discussions that we're having and the agreements that we're reaching this morning have on post approval changes?

And the answer, from an Agency perspective, is the following. We will try to be consistent pre and post approval. That was the whole point of site specific stability as it was expressed in the '98 draft. It was exactly consistent with what was in the SUPACs.

Right now, SUPAC IR is under revision. And what I will commit to this morning is that the agreements reached here will inform the revision of SUPAC IR and the other SUPACs as they go along.

But we are not explicitly dealing this morning with post approval changes. The guidance, as you probably know, when it is revised will not have the SUPAC information explicitly in it, but rather will be included by reference to the SUPACs to take into consideration the revision process.

So we will not address -- it is not my

intention at this time to address post approval changes in the final stability guidance, but rather to see those addressed through the SUPACs.

DR. KASUBIK: Okay. Well, you know, this sort of addresses the comment that Dr. Juerssi had brought up about a virtual company being able to get approval and then later on going to a different site for manufacturing, and that was the reason why I brought this up.

DR. SEEVERS: Well, I think that going to a different site proapproval for an ANDA should be consistent for an NDA. I would like to see consistency of the post approval changes process with what we're discussing this morning, but that's a very big step to take and I don't know that we're necessarily ready to commit to that.

We are going to work toward that end. But being a good Government employee, I can't promise that this morning.

CHAIRMAN BYRN: One comment from the floor. We're talking about post approval issues now.

DR. POLLOCK: I want to make sure I

understand this. Most of the discussions here have been centered around moving from a pilot plant to a commercial facility. I think what we're hearing now is we're going from commercial facility to commercial facility, and I want to make sure that everybody is aware of that in the discussions.

And if there's a distinction that needs to be made, the subcommittee should recognize that.

CHAIRMAN BYRN: Could you identify yourself for the recording?

DR. POLLOCK: Sure. Bob Pollock, Lachman Consultant Services.

DR. SEEVERS: I agree, and I think the principles should be the same. What I'm trying to get across is that in the development of regulatory policy, we need to take things one step at a time. The charge given to this subcommittee has been to address the issue of site specific stability as it is implemented in the draft stability guidance.

The draft stability guidance, when it becomes final, will be focused primarily on proapproval issues. The majority of the post approval issues will be

dealt with in the individual SUPAC guidances.

The SUPAC IR revision is ongoing at this time, and we will see to it that the Agency's policy is consistent. That's really as far as I can go this morning.

CHAIRMAN BYRN: Tony

DR. AMANN: Tony Amann, Eon Labs.

I did want to bring up that one point about the pilot to pilot versus pilot to plant. In the generic industry, in the majority of the cases, the pilot plant is the manufacturing plant. So when they're making their biobatches, they are actually doing it in the manufacturing site.

So, to us, they're pretty much analogous.

CHAIRMAN BYRN: Thank you.

Any other comments?

Okay, I think, as far as I know, I think we've completed our agenda. I'd like to thank everybody for the spirit of compromise. I think this is an excellent example of how industry and Government can work together to achieve goals that protect the public health, get drugs on the market faster.

And so thank you very much for attending.

Bob, do you want to say something?

DR. SEEVERS: Before everybody packs up and goes, I'm the one who's got to go back to the stability committee and put into effect -- take into account what we've talked about this morning. I want to be sure that we have a consensus on the committee.

So can I go through point by point what my understanding of our discussion has been today --

CHAIRMAN BYRN: I think that's a good idea.

DR. SEEVERS: -- and see to it that I have a consensus from the committee?

CHAIRMAN BYRN: Okay.

DR. SEEVERS: Number one is that of the three proposals, the first and third are workable and have different usefulness for different firms. Some firms may choose one, some firms may choose the other.

And the committee consensus was that they would be useful offered as alternatives, recognizing that individual cases may have yet other possibilities, but these would be the two main alternatives.

Is that a correct understanding?

CHAIRMAN BYRN: Okay, so what is being said here is the second -- the hybrid proposal is off the table. The first and third proposals would be -- first would be primary, second would be alternative.

Everybody agree with that?

DR. REYNOLDS: I want to make sure I understand the third proposal with the caveats that we presented from the PhRMA position. That's how you're explaining this?

DR. SEEVERS: That's correct. That would be the primary, the FDA tiered proposal --

DR. REYNOLDS: Right.

DR. SEEVERS: -- as amended, based on public comment, would be the alternate proposal.

CHAIRMAN BYRN: So the PhRMA proposal would be the -- except the primary proposal, the original three tiered FDA proposal as the alternative, and the hybrid proposal's off the table.

DR. SEEVERS: Okay, that's the first point of consensus that I wanted to be clear on.

CHAIRMAN BYRN: Everybody on the committee, do you want to -- do we need to have a show of hands?

MR. LACHMAN: That's the PhRMA amended one that we amended during discussion.

DR. SEEVERS: Correct. I'm going to talk about understanding of the amendments to make sure I'm clear on that. What I want to do is just go through this point by point and make sure that we all have consensus.

And Kimberly, if anybody disagrees, speak now or forever hold your peace. Sounds good.

Okay, then the second point would be the issues related to PhRMA's proposal. The initial proposal we received in the pre-NDA package included a validation summary. PhRMA's proposal does not.

And as we talked about in the conversation between Toby and myself a few minutes ago, the three things that would then be included in the -- let's call it the amended PhRMA proposal -- would be, number one, certificates of analysis of the three validation lots or the equivalent, and making the point that Eric had made that if there are numerical values available, they would be presented and not the word "passes test."

The second thing that would be submitted would be a certification that the validation process had

been completed successfully. And as Leon noted, as part of that, any changes to regulatory in process controls would be noted.

That's my understanding of the -- call it the modified PhRMA proposal, which would be option number one. Okay, --

CHAIRMAN BYRN: Okay, committee, any --

DR. SEEVERS: Yeah, the next question is timing. PhRMA's proposal, as Toby presented it, is that this would be phased in.

In year one -- and we'll date from the release of the guidance as final -- firms would be committing to submit these data a month before the user fee goal date; in year two, two months; and in year three and beyond, three months.

Is that correct in terms of the timing that the committee feels is reasonable and appropriate?

CHAIRMAN BYRN: Okay, committee, does everybody agree with that? Okay, we have a question from the floor.

MR. CLARK: This is Bob Clark again from Novardis. Just one -- a little thing about the in

process controls. Again, the limits for the in process controls are not changing. If the methods change somewhat, that's not that relevant, is that correct?

DR. SEEVERS: Well, the methods are not, per se, regulatory methods --

MR. CLARK: Okay, that's good.

DR. SEEVERS: -- submitted for validation.

MR. CLARK: That's good.

DR. SEEVERS: But I think you need to use reasonable judgement. If you're changing from an HPLC to a TLC method, we probably want to know about it.

MR. CLARK: Okay, that's fine. Good.

CHAIRMAN BYRN: Okay, a comment from the committee.

MS. MALIK: I would agree that that was the proposal that PhRMA put on the table. I guess just for my clarification, based on an earlier comment you made where -- and maybe you're going to get to this where you talked about -- I had talked about the different timing for a long term for other companies.

The impression I got was you might be willing to consider it. Not committing you, but that

part of the understanding had to be that we met the primary stability data requirements that were outlined in ICH.

I just want to make sure I understood that.

DR. SEEVERS: I'm very glad that you brought that up. A proviso for actually either of the two options is that in the initial NDA submission, the full ICH data package be provided. And I heard consensus both from the committee and from the floor on that, and I'll take that as part of the committee's consensus today.

CHAIRMAN BYRN: One question.

DR. CHEN: Sounds like this proposal three is going to be the first choice recommended by the committee. I just want to make sure that everybody is on the same page. When using this as -- when recommending this as the first choice, are we saying this applies to all dosage forms and all drug substances?

DR. SEEVERS: That was my understanding.

CHAIRMAN BYRN: That was mine also.

DR. SEEVERS: In regard to the Agency tiered proposal, my understanding/commitment is that we will use public comments, both those heard here today, as well as

those in the docket, to examine which dosage forms belong in which category to deal with the question of inherently unstable and provide a better definition there, and that that proposal would be revised according to public comments received.

Is that the committee consensus?

CHAIRMAN BYRN: Yes, as far as I know. Okay.

DR. SEEVERS: Okay, I think that that's all the agreements that we have.

CHAIRMAN BYRN: And everything applies to both drug product and APIs?

DR. SEEVERS: That is correct. The one other point that was made is what about post approval changes. And the point -- the response that I gave was that that would be dealt with in the individual SUPACs, but that we would commit to making things as consistent as possible pre and post approval.

Does the committee agree with that?

CHAIRMAN BYRN: Okay, any other -- any final comments? Okay, then I can make my little speech again. I think it's an excellent example of cooperation of the

industry and Government to improve public health.

Thank you all very much for coming.

(Whereupon, the proceedings were adjourned at 11:07 a.m.)

1