

DR. NASR: If you'll allow me, I would like to make some general comments and statements. First, I would like to thank Steve and the working group. You have been working very, very hard, and very diligently, trying to get this document out. Because they understand the need of such a document, and its potential ability to facilitate submissions and so forth. The document is not out yet, and it's not because of Steve. I am the one to blame. So if you have any problem or an issue about the document not being out, please don't put the blame on Steve and his working group, because they are working very hard.

I am holding the document for a variety of reasons, and I would like to share with you, and I would like to seek your input. The main -- the original focus of this document was to create a guidance along the same lines of a guidance for large molecules. And it is very much embedded in the regulations, and regulatory policies, and so forth.

When I came to the Office about a year ago and started stirring things up a little bit. And I started asking many questions. I was troubled by many things, such as the original draft, if you recall, would have meant in many cases of increasing, or to be more quantitative, duplicating the number of supplements. So rather than having a supplement to make a change, now you submit a supplement that we are calling comparability protocol, to be followed by another supplement to make the change. The main advantage could have been that you can implement the change without waiting for the approval for the second supplement. But you cannot get the change going until we

approve the first supplement. That's the problem I have. Another problem I have, it would have very much doubled the workload that we have for our staff.

Number three, which is the major issue, the first two we can handle. And Steve has been working very hard to address these two issues. But the main problem I have, the way the draft has been, and the comments we have received, do not really articulate our current thinking. And if you look at what the guidance is, a guidance is not a regulation. It's a way for us to share with you our current thinking, and suggest ways for you to provide the information for us, for proper assessment in order for you to continue to manufacture products. I don't think of a guidance the way it was, before I came to the Office -- so again, don't blame Steve, blame me -- does not really share our current thinking.

What's our current thinking? I think Ajaz has tried for years, for a couple of years at least, to articulate that, and we are still debating and trying to define the desired state.

DR. HUSSAIN: It's define, Moheb.

(Laughter.)

DR. NASR: Right. Explain what it means for different scenarios, and so forth. What we are saying is if you understand your process, if you understand your product, and you have built enough data, generated data, because of the design of experiments and other experimental protocols, and statistical methodology used, and you have defined the space that you have seen in John Berridge yesterday, and Ajaz and

others as well, where we are comfortable that within that defined space the quality of the product will not be compromised.

In our current thinking, in the new paradigm if you wish, it is up to you to make and implement these changes. You don't have to come to us and say 'I'm going to make that change. Is it okay? Do I need your stamp of approval? How am I going to deal with our inspectors?' What we are telling you is since you have done your work, you understand your process, you understand your product, go ahead and make such a change. And it doesn't have to be a change from prior approval supplement to CBE-30 or CBE-0. And that's where we are struggling with this.

A few other points I would like to make, and after I make my points I will appreciate for you, Judy, and your colleagues to provide us with comments about how can we make this document as useful to you as possible to facilitate the process. Not necessarily to -- not only to reduce the filing categories. I have a problem with my eyes, that's why I have to take my glasses on and off. I'll fix it tomorrow. I mean it.

What we are trying to do with this guidance now is very much to bridge between the existing system, or the existing paradigm, and our future thinking. And that's the reason for struggle. I think in our future, the new paradigm, the idea is not to reduce regulatory requirements, or filing categories. It is to look at ways to possibly eliminate supplements altogether. And that's some new things. And you know, we need to hear from you how we go about that. And I think hopefully the comparability protocol in the final draft after I'm done with it, may provide some ways to facilitate this.

Because we received a lot of comments on this guidance, Steve and his working group have been working very diligently trying to do two things: to expand the guidance to address all the issues raised by the public. That's number one. Number two, to provide more details and examples of when to use it, and when not to use it, and so forth. I think this is very good and noble, but it resulted in increasing the volume of the guidance to become quite a bit. Useful, but more descriptive than I like. So we are working on a compromise, and Steve and I have been working very closely with this, along with people in this immediate office, in making the guidance brief but useful. I think we would like to make it useful, but at the same time there is no reason to make it extremely detailed because I can assure you, no matter how many issues we cover in the examples we illustrate, it will never cover everything. So why not even try. Why should we try.

And I think at last I would like to hear from you, and I hope you focus your comments on what you like to see in the final draft of this guidance. We are working very hard, but we have some internal struggle of how to make the guidance useful, and to bridge between our current regulatory policy and our future paradigm, and facilitate the transition from the existing system into the future regulatory process. Thank you.

CHAIRPERSON BOEHLERT: Okay. Moheb has asked us some questions on how FDA may make this guidance more useful. And I'd be happy to listen to committee comments. Any comments? Gerry?

MR. MIGLIACCIO: First, Moheb, I very much liked what you just said. I guess you expected that.

DR. NASR: I'm surprised, Gerry.

(Laughter.)

MR. MIGLIACCIO: Clearly, a single-use comparability protocol is going to have limited utility. The firm is going to have to prepare two supplements basically, and you're going to have to review two supplements for single-use. Much more utility for repetitive changes. And the concern has always been the specificity may limit repetitive-change use. So, that's certainly one thing that we do see a very good use of comparability protocol for repetitive changes, but how specific does it have to be defined, and how broad can the applicability be. So that's one.

But I think you hit it. You know, John Berridge talked about the design space, the variable space yesterday. We have to figure out a way to continue -- what's the process for first defining it in the original NDA, and then continuing to build it. And as it builds, to continue then to build in the flexibility to make changes without any supplements. That's the process we have to nail down. And it would be ideal if that could come out. But I think you will see firms who choose to do this, and to continue to build that design space, will need some way to get that in to the NDA and reviewed so that they can expand the design space and make those changes. So that is something that we'd be looking to discuss, the mechanism for doing that.

CHAIRPERSON BOEHLERT: Dan?

DR. GOLD: I am very much in favor of the vision that I think you are trying to put forward. And I must say I frankly did not understand why -- if a fully thought out comparability protocol, fully defined, with all the parameters clearly specified, all the data be gathered, fully specified, the acceptance criteria completely defined, if the firm achieves

what they say they will achieve if they do the study, I could not understand why I would then have to put in another document such as a CBE-30 or a CBE. I did not understand why I would not be able to go to an AR immediately. Because if I have clearly defined all the requirements that I will meet, and then I do meet those requirements, and your staff has accepted all that in advance, why not be able to go all the way? So I am very much in favor of the vision that you are trying to move toward.

CHAIRPERSON BOEHLERT: G.K.?

DR. RAJU: I agree with the comments that were made before. I just wanted to raise two points. You can choose to make them irrelevant if you don't agree, and don't want to think about it further.

If we allow a rapid transformation of the manufacturing system over the next two years, and we greatly enhance the capability, and in doing so increase the amount of supplements rather than decrease it, is that a bad thing? I move on.

Number two, is the right body of unit the number of supplements, or the quality of the supplements? And isn't that -- once you make it consistent with the vision, shouldn't the focus be on quality per supplemented -- time per supplement, rather than number of supplements. I agree with everything, but those are the two points.

DR. NASR: I think you are raising a very good question, and I want to make that very clear. I'm not saying that time will come where we will eliminate all supplements. I think what we are trying to work on is to justify the need of supplements for considerable changes that cannot be evaluated at the manufacturing site. I mean, if you make some minor changes that will not impact the quality of the product, the process

remain under control within that defined space, why do you have to come to NDC? I don't want to see you. Basically go ahead and implement the change, since you have laid out early on your experimental design and how you are going to control the process, and the parameters are well defined within that space. There is no reason for supplement.

However, if you elected to make a major change that may impact for a change in the specification, or may require evaluative study. Where we are getting to potential clinical impact, this may be a time where you can propose the change and bring your experimental design to us for an assessment to make sure, because we have a responsibility to the public that the change you are making, the major change you are making, will not adversely impact the quality of the product as it is related to safety and efficacy. That would be the only time, in my mind, where a supplement is needed. If you are changing a lubricant on a seal on a filling machine, I don't think you need to come to us with a hundred supplements to do that.

DR. RAJU: So we won't get to a place where there's zero supplements, but getting there means first increasing it before it goes down. How are we going to find out?

DR. NASR: I think our role will be to facilitate continuous improvement. And some of this continuous improvement can be done without any regulatory oversight, and some may still need some regulatory oversight in the form of scientific dialogue to have an assurance what you do is scientifically sound.

MR. FAMULARE: A question I might raise to Moheb and Steve. If the change is bringing you closer to the specification, or closer to the design space, as

opposed to you're further away from it, then could we -- is that an area of no supplement?

Is that how you're looking at it?

DR. NASR: I think, if I hear you correctly Joe, you want to change the space. And you are saying 'Are you willing to expand that space?' I think that will be something that we need to look at.

MR. FAMULARE: Well --

DR. NASR: But, but -- just let me finish, please. But, if we agreed on that space, and that's the data, and this is the scientific model you have, you can go ahead and make the changes within that space. If you come and say, 'Well, I'm going to expand the space, and instead of having that oval-shaped, I'm going to have some points scattered around and generate another geometry, if you wish,' this will be a time where we need to sit together and see the impact of such a change on the space, on the quality as it relates to safety and efficacy.

MR. FAMULARE: Right, what I was thinking of is if you're going beyond the space, your process is drifting beyond the space and then the change brings it back in, is that something that you want to see?

DR. NASR: No.

MR. FAMULARE: Right. And I think that would make a good corollary to the Q10 and how -- the Quality Systems, and bringing things towards continuous improvements. And I think eventually this will correlate with that.

DR. NASR: Some people, however -- I know you don't -- but some people, however, think of the concept of continuous improvement, that there will be no

regulatory oversight whatsoever. I think we need to minimize regulatory oversight to facilitate continuous improvement, but there will be some key elements that must be integrated, must be presented in a coherent manner. And these are elements that may require evaluation assessment, good Quality Systems to manage the process of the plant, a good GMP inspection, and defined space regulatory processes. All these things need to be together.

MR. HOROWITZ: I don't disagree with anything Moheb or Joe said. I agree completely, and I just wanted to echo a couple of the sentiments.

Continuous improvement doesn't require the absence of all regulatory oversight. I think we all agree with that. Our system intentionally has redundancies built into it. And that's a good thing in terms of protecting the public health. Sometimes it can get in the way of continuous improvement to the extent those redundancies become burdensome. And it's partly our job to identify areas where we could do without some of those redundancies. And I think there's often overlap between the safety oversight and the benefits on the review side, and the safety net that we have with Quality Systems and with GMP oversight. And there are certain instances where we could take the chance, if you will, as regulators, to give more flexibility to the regulated industry to make changes, knowing that if something goes wrong, there are other safety nets. There's a Quality System in place. And if we get more assurance that the Quality System is effective not just to prevent errors, through change control and other things, but also to be able to detect them, to detect them in a timely fashion.

And I think that's what Q10 is really about. It's about giving the regulators more confidence in the ability of the Quality System to serve as that safety net, to give us greater confidence and greater ability to remove some of the redundant oversight that may have been in place on the review side.

One last point. It all comes back to specifications, though. We could have all the Quality Systems in the world, but once the specifications, as part of the QA process, become more rational, more clinically based, I think we can ultimately have greater confidence in the ability of enhanced Quality Systems to catch real problems that affect the clinical -- of clinical significance that would affect the patient. And I think that's all part of the desired state. It's going to take awhile to get there because there are a lot of pieces that need to be put in place. And things like Q10 and other aspects of this require a bit of a leap of faith for all of us, to be willing to say 'We can't be sure whether this is ultimately going to have the payoff we're expecting, but we've got to build a foundation if that might happen.' It might not be a sufficient condition, but many of these things are necessary conditions to move forward to the desired state. Thank you.

CHAIRPERSON BOEHLERT: Any other questions or comments?

Gerry.

MR. MIGLIACCIO: David, the way you've described Q10, obviously we agree with. The question is if we don't get the support in ICH for Q10, it has to happen here. So we need a contingency plan, as we're still not assured that it will move through. It's not approved yet to move forward.

DR. HUSSAIN: It has been accepted. I mean, the timing of that is going to be just --

MR. MIGLIACCIO: The timing.

DR. HUSSAIN: A step of when Q8 and Q9 goes to Step 2. That's the timing. It's a timing issue. I think we supported it throughout the process, and we leave it to our regulatory colleagues from Europe and Japan because of their resource issues. So I think the steering committee has accepted it.

CHAIRPERSON BOEHLERT: Are we ready to move on?

MR. FAMULARE: I just had one short comment, that I mentioned over the course I think of yesterday, that we have this Quality Systems guidance coming forward, and it's more broad than Q10, but certainly comments to that guidance when it issues in September can certainly latch on those things here, and get it moving. And it may spark movement also in ICH.

DR. NASR: I just want to add one thing in response to Gerry's question about Q10 implementation and timing. I think it's a good thing it will have a global agreement of the goals of Q10 and how to get there, but I think we internally here at the Agency have decided to move on. So we are making some drastic changes now, both on the review side and the inspection side to facilitate continuous improvement. And we are very serious about that.