DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Wednesday, October 20, 2004

8:30 a.m.

CDER Advisory Committee Conference Room
5630 Fishers Lane
Rockville, Maryland

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Hilda F. Scharen, M.S., Executive Secretary

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Joseph Contrera, Ph.D.
Ajaz Hussain, Ph.D.
Monsoor Khan, R.Ph., Ph.D.
Steven Kozlowski, M.D.
Vincent Lee, Ph.D.
Qian Li, Ph.D.
Robert Lionberger, Ph.D.
Robert O'Neill, Ph.D.
Amy Rosenberg, M.D.
John Simmons, Ph.D.
Keith Webber, Ph.D.
Helen Winkle
Lawrence Yu, Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. KIBBE: Ladies and gentlemen, I would like to call the meeting to order. The first item of business is the reading of the Conflict of Interest Statement.

Conflict of Interest Statement

MS. SCHAREN: Good morning. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such.

Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability and there are no products being approved. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All Special Government Employees have been screened for their financial interests as they may apply to the general topics at hand. To determine

if any conflict of interest existed, the Agency has reviewed the agenda and all relevant financial interests reported by the meeting participants.

The Food and Drug Administration has granted general matters waivers to the Special Government Employees participating in this meeting who require a waiver under Title 18, United States Code, Section 208.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Because general topics impact so many entities, it is not practical to recite all potential conflicts of interest as they apply to each member, consultant, and guest speaker.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to disclose that Dr.

Paul Fackler and Mr. Gerald Migliaccio are participating in this meeting as non-voting industry representatives acting on behalf of regulated industry. Dr. Fackler's and Mr. Migliaccio's role on this committee is to represent industry interests in general, and not any other particular company.

Dr. Fackler is employed by Teva Pharmaceuticals U.S.A., and Mr. Migliaccio is employed by Pfizer, Inc.

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' 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 product they may wish to comment upon.

Thank you.

DR. KIBBE: Thank you.

Yesterday, we concluded with a suggestion that we might want to continue our discussion about the questions that the Agency has raised, and I think Dr. Meyer has asked Dr. Hussain to come up with a straw man, and we have it ready, so I think we should go there first and then go back to the scheduled agenda.

Ajaz.

Committee Discussion (Continued)

DR. HUSSAIN: Good morning. I think the discussions towards the end of yesterday started honing down on some of the key challenges we face in the designing of a Critical Path Initiative in OPS.

I think, reflecting back on the discussion yesterday, clearly, I think we have a wide range of research capabilities and programs already in place, and the challenge would be to sort of direct these in a very focused way to help the Critical Path Initiative, keeping in mind that all of our research will not be focused on critical path, there are other aspects that we have to focus on.

I will sort of reflect back on the PAT Initiative and how that sort of evolved. Clearly, if you recall, the PAT Initiative led to the GMP, and there is a whole sequence of initiatives that have occurred. The PAT Initiative was a model and we can learn some things from that as a model also.

I will sort of summarize my thoughts here with a hypothesis statement that Jerry proposed yesterday, that Critical Path Initiative will improve the efficiency and effectiveness of drug development process. That is the hypothesis that sort of really we are engaged in trying to fulfill or trying to confirm.

The challenge would be then how do we measure efficiency and effectiveness of drug development. That is one of the keys, how do you measure drug development in terms of the failure rate, or the time it takes, or the cost of drug development.

All of these are relevant metrics, but for the purposes of a hypothesis, what and how should we approach and define that, because unless you can

measure something, you cannot improve it. So, measurement and metrics would be a key factor of that.

The second aspect then would be what are the root causes of low efficiency and effectiveness in all the three dimensions. A number of factors were put up looking at 1999 or 1991 or 2000, and so forth.

They were indicators of what may be happening, but you have to keep in mind that is partial information, information available to FDA and available in public is just limited because the companies have far more information about the root causes, and so forth. So, you have to sort of factor that into our decisionmaking.

The next question is who is in the best position to address these root cause factors that we identify, what is the role of FDA, what should FDA do and what should some industry, academia, and other agencies should be doing is the key there.

I think based on information and based on experience at FDA, clearly, we are in a good

position to identify many of the problems, not all of the problems, but many of the problems, and FDA has the responsibility to communicate these findings in some way or form.

If you look at John Simmons' presentation, he laid out, as a part of the critical path, strategic meeting points during the drug development process. That is one aspect, communication between sponsors of applications and our review scientists, if that is timely and in a coordinated manner, that is one effective means of that.

So, communication through meetings for specific drug applications, broader communications with workshops, and then eventually guidance documents outlining FDA's current thinking on a given topic are the communication mechanisms that we have.

For that, clearly, I think you have to think about resources and how do you facilitate that process. If you want to sort of move towards more meetings and more interactions between

reviewers and sponsors, then, you have to build the time for that, and so forth. That has to be considered, too.

Workshops and guidances also take a significant amount of effort, and so forth, so as we improve our communication channels, where will we find the resources and time to do that, I think that is also a management aspect that has to be discussed.

FDA's knowledge base, I think was clearly an asset in the sense we have a lot of information. If we are able to create a knowledge base that can be useful, not only for identifying problems that we see, but also for improving of a predictive ability in all three dimensions, safety, efficacy, and industrializations, what are the practices that lead to success, what are the practices that may not be as efficient, and so forth.

So, this knowledge base would be useful for that purpose, but again I will remind in the sense we have to be cautious, there are limitations of that knowledge, because we don't always have all

the information, so you have to factor that in.

But based on our knowledge base and based on communication, and so forth, I think the laboratory and the research functions clearly have to focus on improving methodologies. There are many aspects of laboratory work that only FDA is in a good position to do, and others either don't have the interest or don't have the focus to sort of address some of the challenges.

For example, in the case of regulatory decisionmaking, risk-based decisionmaking, the decision process itself often needs support of science, and so forth, so that is where the research really could focus on.

Also for development and validation of new methodologies, standards development, methodology, validation, say, from biomarker to any new technology, unless FDA has a role in achieving that, it may not be fully appreciated within the Agency, and some of the Agency concerns would not be addressed if it is done totally outside, so there has to be some means of linking our

laboratory work to standards development, validation of new methods, and so forth.

Our postmarketing experience again is unique because that is where I think we have a lot of information, how do we capture that as lessons learned and how do we use that. You saw some examples of how we were learning from that and going retrospectively and said how could we have improved the process. Those experiments would be very valuable.

One aspect is in terms of innovation, in terms of new technologies, what is an important aspect of standard setting? Standard setting and guidances are slightly different in my opinion. For example, in the PAT Initiative, we opted to move towards ASTM International as the body for standard setting.

What that does is allows industry, academia, every stakeholder to be part of that, and actually identify what standards are needed, and actually develop those as quickly as possible.

That relieves the burden on FDA, and FDA

simply adapt or adopt those standards after evaluation, so that might be an option that seems to be moving forward in the PAT Initiative for new technologies, new methods, and so forth. So, that could be considered at the same time.

But at the same time, I think as we look at FDA's role, what is the role of industry and what is the role of other agencies and academia really have to sort of come together.

The role of industry I think is knowledge sharing. Clearly, it has far more information, and reluctance to share knowledge will inhibit the progress, and how do you do that is a key challenge.

At the same time, I think in order to bring all of us together, focused on a given goal, we really I think have to define clearly the metrics, the desired state, and so forth, and come on the same page, so that we can coordinate all of these activities.

In some ways, FDA could play that role of coordination, as Viad declared yesterday, not only

from the prospective of we are not competing in this arena, eventually, we have to be involved, so coordination function for FDA would be an important function for all these activities.

If we have a clear understanding of what are the issues and what are we trying to achieve, then, the coordination and synergy would sort of evolve naturally.

So, those are the sort of thought process that I could capture.

DR. KIBBE: Anybody? Marvin? You asked for the straw, you got the straw man.

DR. MEYER: The virus, are you talking about that later?

DR. HUSSAIN: No, that is a very specific example.

DR. MEYER: I thought I had more time to think then, since I was waiting for the virus.

DR. KIBBE: Does somebody else want to--

DR. MEYER: No, no, I have something to say.

DR. KOCH: Marvin, just before you--I

think I need a point of clarification because some of what came out yesterday was the desire to have either shorter development time, more compounds coming out that could be effective, new pharmaceuticals, and it seems to be a push towards industry to try to become more effective, et cetera, but I saw a couple times yesterday where things developed within the Agency to improve the ability to go after materials through some of the databases and things were certainly ways to help that process.

The other thing, though, is that when you looked at that chart that showed an increase in cost of materials and a few other things, toxicity, you know, is something that shows up there, and I think something a little bit insidious over time has been with improved technologies and increased concerns over pharmaceuticals, there are new tests that come in that prolong the evaluation, that anything the Agency can do to pull things together to make those things, immunogenicity or other things that have, you know, you go back two

generations ago and if you come up with a new material, would you put it through all of the same tests, so anything that can be done to simplify and do more predictive studies in that regard, I think would help.

DR. HUSSAIN: Definitely, that is an important point. For example, I think as we move towards more complex materials, the material cost is, as you saw, is already showing up, and so forth.

Introduction of new excipients or new adjuvants, and so forth, is a significant challenge, and as we go towards nanomaterials, nanodevices, and so forth, if we still have to rely on the traditional pharmaceutical excipients, it would be a very limiting aspect, so I think that that is clearly on our agenda.

One aspect that I do want to mention, as we think about this, the patient has to be foremost in our minds, what are the unmet needs, and as we sort of develop this, I think clearly, the patient needs have to be kept in mind as we move forward,

because there are many diseases, many aspects where we don't have effective drugs, and so forth, so we shouldn't forget that aspect.

DR. KIBBE: Marvin, are you ready now?

DR. MEYER: Yes. I was just thinking of a simple example where the Agency I think played a major role and really expedited drug approval, and that was back when we were battling over assay method validation.

The hypothesis was if we had a better way of validating assays or a uniform way of validating assays, things would get approved without recycling and redoing, and, in fact, FDA then, and APS and others, convened several workshops, had white papers, ultimately put out a guidance, and I suspect that hypothesis has been tested, that there are much fewer problems in the local methodology, so I think that is a good model, and you alluded to that.

DR. KIBBE: Anybody else would like to make a comment?

DR. SINGPURWALLA: Yes. I repeatedly hear

from individuals like yourself asking industry to share more information with you. What is the incentive to the industry to do so, because there is a penalty to do so? Recently, those of us who read the Washington Post can see the number of pages devoted to the Merck and also to Pfizer having a similar drug going to be tested, and things like that.

So, unless the legal pressures that are on industry are defused or removed, industry is going to be foolish to share all the information with you. I wouldn't. It's like me going to the IRS and saying look, this is how I have cheated, catch me. It doesn't make sense, does it?

DR. HUSSAIN: No, I think it is not in the context of sort of cheating, and so forth. This is in the context of how much we know and how much we don't know, to start filling the gaps where the knowledge exists. Clearly, that is the aspect, and it is complicated by the fact that the way it gets entrenched into the legal and political scenarios, those are significance challenges, no doubt about

that.

DR. SINGPURWALLA: What is the industry's response to this?

DR. MIGLIACCIO: Well, it is complicated by obviously, intellectual property rights, which is the life blood of a commercial business, but it is also complicated by--you just used the word "trust."

I will give an anecdote here. I went to an internal FDA meeting to provide training, and during that training, provided knowledge about products, which normally, would not have been made available.

The reaction was the traditional predictable reaction, not the forward thinking reaction, by certain elements of the audience. So, that was a risk, that was a poorly thought-through risk on my part.

We have to reduce the risk associated with sharing knowledge. That is the fundamental issue is if we share knowledge and expose ourselves to compliance action where that knowledge is

essentially reflecting what is the scientific truth, and we can now measure that, we can now see that where we couldn't before, and if you divulge that knowledge and risk compliance action versus scientific discussion, then, the knowledge will not be transferred.

DR. KIBBE: Ajaz, anything?

DR. HUSSAIN: No.

DR. KIBBE: Anybody else? Let me just put three things on the table and perhaps you can think about them as how they respond to the questions we were left with yesterday.

One is that I think I heard from around the room that the Agency has a limited resource base, and it truly should focus on those aspects of the critical path that only the Agency can do, that no one else has the wherewithal or the capability or the information to do that.

Secondly, that we try to get others who are even more capable of responding to certain aspects of the critical path to take on that burden. I am thinking primarily of industry and

perhaps industry/academia together looking at those aspects of it.

But the third thing that I think that the Agency and both the industry will have to look forward to is that the rate of technological advance is such that 10 years from now, the questions that you are trying to answer now will be ancient history, and the questions that you are running into are going to be dramatic and clearly different, and I really look forward to a paradigm shift in the way we approach therapy, and I would recommend to the industry that they change their name from drug companies to companies that provide therapeutic agents and processes, because they could be caught up in the same system that the railroads did. They were railroad companies, and not transportation companies.

I don't know how the Agency can respond effectively without having some type of internal committee that is constantly looking at four or five years out and the technology that they are going to have to deal with then.

So, that is where I think the critical path kind of initiative ought to be looking.

DR. DeLUCA: Let me just comment. I made some notes here from yesterday, and I think that this is based on collaboration, I think I am going to really focus on that, and as Jerry mentioned, I think trust. Certainly, trust is essential in collaboration, and as we get into talking about the science-based approach here and research, research is a search for the truth.

I would like also to commend the Agency in their research efforts. I mean yesterday was, I think, I would say overwhelming to learn the type of research that is going on and the collaboration with NIH, so I really have to commend the Agency for this.

I would like to also talk about the presentation by Monsoor Khan where he talked about critical path research and some of their efforts, and I think Gerry Migliaccio had responded that industry takes this approach.

I have to say that that is true from my

experience to an extent. I know, I am involved in the novel drug delivery area and the research in that area, and working with a company that was scaling up or transferring some technology, that that approach was taken, the critical path approach was taken, and worked with them, and they did solve the problem at hand, but there were other things that still needed to be done to define some of the process variables, that once the problem was solved, they went on, they didn't want to go any further with that.

So, I think there is a limit to where they go and I think this is where collaboration is important, and I think there is a need to continue on and to search those things out, and probably the place for that is in academe.

I don't know if it was Jerry Collins, when he talked about the science-based approach to critical path issues and the research, that it is probably essential that the research that is going on, that it is going to be hypothesis driven. I think this is something that many times the

research that takes place, and if it is in an industrial setting, may lack the hypothesis driven type of research, and that probably I think is important.

I guess my feeling is in hearing all the things, and I think what Art had said, FDA can't really overreach, I mean there is a limit resourcewise, but I think more importantly is the idea that they can't do it alone, so I think that collaboration is important.

The FDA has been collaborating more with NIH, and I think translational research issues, taking the drug product development, that portion of it along, but I think there is a gap there with the critical path, in the formulation and taking it and the manufacturing science, and I guess I think that the collaboration has to be there between academe, industry, and FDA, and FDA could really set the stage for this. I think there is a very important role.

Just to bring out my experience with the journal, the APS on-line Pharmaceutical Science

Technology Journal, that the submissions, we get about 50-50 from abroad and the United States, but about 90 percent of the submissions--now, this is in the Pharmaceutical Technology Journal, and you would really think that you would get more from industry--but about 90 percent of the submissions come from academe.

I have to acknowledge that probably in about 40 percent of those, there is a collaboration between academe and industry, so that there is a tie-in and that it is all those being submitted from the academic institution, the industry is involved in it.

But I think that this kind of sends a message, and I have tried to encourage more, more submissions from industry, and there is intellectual property situations involved in that, but I think there is a need.

I know, being in academe and graduating Ph.D.'s, the majority of them will go into the industry, few of them publish after they are in industry. Before they left, they had eight or nine

publications, and then they went in and stopped publishing, so, I am not sure that is a good thing.

What I wanted to emphasize here is that there is an essential need for collaboration. I think the whole science-based approach to the regulatory arena is great, and I have to commend the Agency in this, but they just can't do it alone, and I think there is an essential need that this collaboration occur.

It may be that with that type of collaboration, you know, for a long time in academe, we have talked about the NIH and trying to get them involved with supporting drug product research and development to little avail, so maybe now is the time.

Certainly, I think it is essential that this type of approach be taken in the manufacturing sciences, because it certainly will benefit, I think, our society, so I think it is in the interests of the country, so that hopefully, the NIH will look a little bit more favorably on supporting this type of research. I think the

collaboration between FDA and NIH may help in doing just this.

DR. KIBBE: Thank you.

Ken, go ahead.

DR. MORRIS: Thanks, Art. Welcome to your last day.

A couple of things I wanted to say first to Nozer's point. In the face of the data that I think Merck generated or was generated and then shown to Merck, I don't think they would need the Agency to tell them that they needed to pull the drug or to modify it. They are really very responsible about that sort of thing. I understand your point.

DR. SINGPURWALLA: The lawyers made them do it.

DR. MORRIS: Well, the lawyers made them do it, but the drug companies in general, the innovators of generics, when they see problems like that, are still I think honor bound and have historically done a good job of monitoring themselves with respect to public health when there

is a clear and present public health injury issue.

But beyond that, let me just comment, if I can, I have just five points here, relatively short.

The first is, is that the unique opportunity afforded by the FDA massive database, I think is absolutely invaluable and needs to be exploited to the maximum. I mean that, in my mind, is perhaps the number one initiative in terms of getting down the critical pathway with all due deference to proprietary data, of course, as we saw yesterday.

There are some issues I think, for instance, tox, where the database would probably not be nearly as good as even the sampling of the Big Pharma companies' databases on tox, because you don't have the tox information on compounds that never made it to filing, so they may actually have a bigger database there, which would really help in the really interesting work we saw yesterday on modeling.

The second point is it look from a

nonbiological and obviously blue collar tablet smasher, that there is a fairly large disparity between the amount of internal biological research versus product development research. I am not really in a position to judge what the priorities in the biologicals should be. It is all obviously, very high-caliber research.

I am not in any way commenting on that, nor am I capable of it, but I think it does point out the fact that there are developmental research agendas that probably would be better handled in part at least, or at least administered through the Agency, that aren't being, and we can talk about specifics, and have with John and you and others, of course.

But I think that points out an opportunity if you were on the critical path, and that is the prioritization that I was asking about yesterday, is that given the breadth of projects and the dearth of resources, I think the prioritization, particularly the internal research projects, becomes your biggest challenge and one that I think

could be helped by the committee, and I think has been in part, hopefully, in these days.

It also points out, to reinforce Pat's point, and this is a little bit self-serving, but the amount of research that doesn't or is not as logically done within the Agency, needs to find federal support in terms of public health initiatives, as well as the obvious advance of just basic science.

To address a question that Gerry had raised with respect to the possible putative consequences of sharing information, there is a mechanism that we have been sort of developing, which is to, through blinded intermediates, to be able to discuss general topics without filtering.

I am not talking about filtering data or hiding data, but to bring data to light to the Agency in a blinded manner to say, you know, is this the sort of data that would be useful, or is this the sort of data that would give you cause to think that there was no particular reason to review it, and it would just be a waste of the Agency's

time.

So, I think there are mechanisms to do that. They are not formal mechanisms, but through consultants and whatnot, I think you have already got that as an opportunity, so you can't be too specific, of course, because once you are too specific, then, you have already revealed what it is you are asking about.

Finally, with a question of metrics, I think the suggestions you made yesterday, the multiple review cycles I think is a great metric. That was what the Manufacturing Subcommittee, at Judy's last meeting, we talked about the idea that in the new or the desired state, instead of having minimal data that the reviewers have to try to piece together into some sort of Frankenstein rationale, if you get the rationale in a piece from the companies with summarized supporting data to make it a compelling argument, then, the reviewers just have to assess the sufficiency of the rationale as opposed to trying to piece together one on their own.

So, I think the review cycles are an excellent metric. The time to approval, of course, is a low hanging fruit there in terms of a metric although it is not independent, and for generics, of course, that is compounded by the workload itself.

Maybe you could normalize it by normalizing the time to approval to the number of pre-filing and pre-approval meetings, the off-line meetings that John talked about yesterday, John Simmons talked about yesterday.

The other one--and I don't know if we have talked about this before--is to track FDA personnel turnover. I think it is not a bad metric to look at retention of the FDA reviewers themselves. I mean it is a very high-pressure job, it is not all that celebrated a position, but obviously of key importance.

I think that does two things. One is it gives us a metric of how effectively the program works, and the other is that it gives an internal metric for the personnel management, so you don't

burn out your best and brightest.

DR. HUSSAIN: Ken, the whole aspect of the critical path was in a sense that review cycles have really come down, so that review cycle is not the rate-limiting step in the critical path. So, there are different metrics for that purpose.

DR. KIBBE: Marvin, do you have something else?

DR. MEYER: A quick comment. Helen was saying last night that on the ANDA side, that the generics are now, or shortly going to be, required to submit all studies they did, not just the 1 out of 12, the test.

Maybe, and this is terribly naive because I don't know all of the complications, but maybe there is some way down the line of having the NDAs be accompanied by a synopsis, at least, of what they tried and what failed, a one-pager perhaps.

We tried doing virus filtration this way, and it failed because, we think it because, and this might be attached with the NDA, but reviewed independent of the NDA. There might be a group at

FDA that evaluates failures, if you will. So, some way of getting the data to the Agency that wouldn't impact on the NDA and yet would provide the Agency with I think some valuable information.

DR. KIBBE: I am concerned that as much as we in academia value getting all the information, industry values having information that their competitors don't have, and if they have a lot of failures they corrected, and they know what mistakes not to make, they generally think they have an edge on doing it right, and they are not really excited about turning that over to someone else, let them make their own mistakes and figure it out.

I think the time that we will actually be able to share all the information about all the drugs that have ever been approved is when Glaxo finishes buying everybody or Pfizer has merged with whoever is left, and there now is International Therapy Development Company.

DR. KIBBE: Ajaz, anything to wrap up with? Okay.

DR. SINGPURWALLA: Mr. Chairman, I have a few thoughts. Ajaz, back.

[Laughter.]

DR. KIBBE: It's okay, Ajaz, you can escape if you would like.

DR. SINGPURWALLA: Ajaz, you asked three questions here. To be quite honest with you, yesterday, I couldn't focus on these because I couldn't get my mind straight as to what we are up to and what is happening.

But subsequently, I think I can answer some of your questions very directly.

I looked at TR Critical Path Initiative Challenges document, and to be quite honest with you, I think you are on the right track, and I think you are thinking along the proper lines.

Two, three things come to my mind. Your mention or at least the mention of design of experiments that was discussed is one of the right ways to go about things.

You also mentioned the use of bayesian ideas. That is the best way to reduce time cycles

because you are taking advantage of all other sources of information, but you don't want to use that only for clinical trials, but you want to use it throughout the entire process. Again, you have highlighted it, so I think again you are on the right track.

The one thing is you cited examples from manufacturing. That is fine, but I seriously consider you also look at the area of weapons development. They face problems very similar to yours and you may want to see what they are doing and how they are developing their particular processes, and the weapon development process has much in parallel. The two communities are very alien to each other, but I urge you to look into what they are doing, and I think I can say that you are on the right track. You are focusing on the issues that I would focus about, that is all. I wanted to reaffirm it.

DR. HUSSAIN: Thank you.

DR. KIBBE: Paul.

DR. FACKLER: Let me just offer a couple

of thoughts to those questions, you know, are you on the right track. Of course, I am speaking for the generic industry, but it is difficult to give people help when they haven't asked for any, and I can't speak for PhRMA, and I don't know if PhRMA has come to the Agency and said, help, we can't develop new drugs.

So, I think you face a very difficult challenge trying to assist a process that maybe the people actually doing it don't feel is broken. The economics of drug development in 2004 is significantly different than it was in 1994.

You know, if you have a company selling $50 billion in drugs a year, and they want to grow by, say, 5 percent, which isn't acceptable by any means, they need to get an additional $2 1/2 billion in revenue out of the new drugs that they are developing.

So, you know, a product that has some marginal value, say, 50- or $100 million that would benefit society probably just gets put in an envelope somewhere, and not brought out. It is a

problem with the situation in industry, but I am not sure FDA is going to be able to do anything to assist that.

Let me speak to the generics because there was a presentation yesterday, and speaking for the generic industry, we have communicated with FDA where we think we need help. We have asked about topical products, we have asked about inhaled products, biologics, of course, are an issue, and time to approval is a real issue for us.

So, the question was are you on the right track, and at least from the generic perspective, the answer is yes. I think you are trying to overcome the hurdles that we face, that would assist us in bringing products to the market earlier.

I know it is not really the main thrust of the Critical Path Initiative, but for our portion of it, the answer is yes.

DR. KIBBE: Thank you, Paul.

DR. HUSSAIN: I think just the point generics are equally important for us, so they are

part of the critical path from an OPS perspective.

DR. KIBBE: Gary.

MR. BUEHLER: Well, we have had a number of mentions of our workload. It is significant. We did receive 563 applications I believe the last fiscal year, 449 the year before, and 361 the year before, so we are increasing by about 100 a year.

It is a bit scary, but we are dealing with it, and we are communicating with the industry significantly on what we can do to make their applications better and to make our responses to them more predictable, so that they know what we want.

As part of the critical path, and we are trying to work in providing the information that the industry needs to develop their products, and this is through the dissolution methods and the bioequivalence methods that we get tons of letters.

We got over 1,000 correspondence last year, over half of them requesting what is the bioequivalence method for a particular drug, what is the dissolution method for a particular drug, so

we can begin to develop our products.

We are trying to get that up as a web-based program, so that they can actually access these methods. We have people working full time in our office to research this information, so we can make it available to the firm.

Now, this isn't revolutionary stuff. This is stuff that we have always provided them. We just want to provide it to them faster. We want to make it easier for them to access this information, and we don't want to get as many letters. The letters that we get obviously take up our resource time, and we want those resources to be put toward application review.

We hope to be able to get these up soon. I know I promised them I think six months ago to the industry. Things are never as easy as you would like them to be in the Agency. A lot of people have to sign off and make sure that we are not giving away the farm, and we don't want to give away the farm, but we do want to give away information that is needed by the generic industry.

The generic industry is a very viable, very robust industry right now. A lot of new players are getting into it, a lot of people want to put applications in as evidenced by our workload. We welcome that workload, we are glad. This country needs generic products. A lot of people out there can't afford prescription drugs out there.

So, we welcome the work and we welcome the challenge.

DR. KIBBE: Anybody else? Okay.

We have an opportunity now to hear from an absolute genius. They asked me to give a talk on visionary overview, and I will get up there, then, I will pontificate for half an hour, and I hope you all enjoy it.

Science in Regulation - Visionary Overview

DR. KIBBE: I need a soapbox. I have six slides. This is to reduce some of the slide overload that we are suffering from. You all have copies of these slides. You can tell that the slides are really informative because they are

filled with words. I look at slides and I say, hey, there are 22 slides and each one has 180 words, how am I going to get through it, so I put up a couple of simple slides.

First, the title was given to me by the Agency. I looked at it and I said Visionary Overview, I guess they think I am a visionary, why would they think that. So, I thought long and hard about why they think I am a visionary, and I realized it was because I live in Pennsylvania, which is the home of the world's most well known and renown visionary, the seer or all seers, the procrastinator for all good things, Punxsutawney Phil, who comes out and tells you whether you are going to have winter for another six weeks or not.

I also would like to make a disclaimer, we do lots of disclaimers. All the ideas that I express today are strictly my ideas, and I would not saddle anyone in the scientific community and industry over the Agency with any of these cockamamie ideas. So, they are all mine and hopefully, they will stimulate your thinking

without putting you completely to sleep.

So, what has the FDA and we been doing for the last few years? I actually went out and got a copy of the agenda for the first meeting I was at, and there wasn't PAT mentioned in the agenda, but when you looked through the agenda, you saw the beginnings of what was I think a wonderful three- or four-year push in an area that can significantly impact industry's bottom line, and hopefully, the industry will be in a mood of generosity and have that bottom line, some of those savings reflected in the cost of goods produced.

The effort I think was an opportunity for me to view the way that scientists from industry, both the generic and innovator companies, scientists within the FDA, and scientists from academia, and those consultants who serve all of us, could get together, look at a problem, develop a reasonable approach to it, something that would work in the community that we work in, and really come up with something worthwhile.

I could go on about the successes we have

had, but they don't make great news, and the news media always wants failures and disasters to report on, and so I will move directly into those.

First, is it the Agency's role to apply science to regulation? Of course, we all agree it is. The application of the scientific method to goalpost generation for the industry is extremely important, and I am going to try to look at what we have done and where we are going, and perhaps make some projections out.

If we are going to regulate a science-based industry with science, then, we need to use a scientific approach to where we are going.

We all are familiar with linear regression, and we know that there is a certain amount of error associated with it, but in order to project beyond the data that we already have, we have to have a significant amount of data going backwards to draw a line through, so that as we go out in the future, we get closer to the truth.

We know that the further out in the future we can project, the less reliable the answer is,

but we do it anyhow, and I am going to do that.

So, where have we been in terms of regulating the quality of drug products and therapies in the United States? Of course, we start in 1817 with Dr. Spalding, and he decided that we ought to get the physicians together and say why can't we have quality products to give to our patients, let's set up some standards, and the USP was formed.

So, we started the regulation of the quality of how we treat our patients by getting the health care providers who treated patients together to decide what quality was and how to arrive at it.

After the Civil War, the pharmacists got together and decided that while the USP had standards for individual ingredients, it really didn't have standards for how to mix them together and make them useful, so they decided to publish the National Formulary, and I was instrumental in the first edition, and I brought my copy with me.

This is the sum total of how to make pharmaceuticals in 1888, and compare it with what

we know today and how many shelves it takes up, and how controversial each little, tiny issue is. Of course, we also know that you have to learn Latin to use this, so it's dead along with the dead language that it is written in.

At the same time, the industry actually regulated itself. There was a comment made here a little while ago, which said that lawyers make them do things. I would argue that in the current litigious society, companies act slower to remove drugs from the market when they have worrisome data than they would if there wasn't a litigious society.

I think they worry more about what it means to their future class action suits to actually admit that there is a problem until they have all their lawyers lined up, so they know how to defend themselves, and if they weren't worried about the fact that the American public has an exaggerated misconception of what drugs do and work, they would act quicker.

I think the American public in general

expects drugs to be safe and effective, and they don't recognize that drugs can be safe and effective if used correctly, but in the wrong way, are dangerous and shouldn't be used, and they don't get that. They just don't get it.

I put E.R. Squibb down because I know a little bit about E.R. Squibb as an example of the leadership that the industry had back in the 19th century. Dr. Squibb, a physician, wanted a higher quality ether for anesthesia. This was an extremely important drug in those days, and so he founded a company for the express purposes of making sure he had high quality ether.

He built it in Brooklyn, and then his company started making other things and then he noticed that there were other companies that were copying his products, calling them the same thing and putting them out there less expensively, and he said the public might be at risk if they aren't made correctly.

So, he did something unique which I don't think any of the companies would do today. He got

all his formulas together, how he made everything, and he published them in the Journal of the American Pharmaceutical Association with the proviso that if anybody wanted to make a product that E.R. Squibb sold, they should make it the way we make it, so it would be of the same quality, so at least the public would have a good quality product, and if they could make it less expensively than we could, good luck to them.

Well, I wonder how many companies are ready to jump into that game. At that same time, of course, Eli Lilly was producing well over 100 generic products. It was the largest generic manufacturer in the United States. It produced everything that could be made that was listed in the USP or NF, extracts, and what have you. It was an interesting time.

Now we get into government regulation. Now, why did the government get into regulation? Well, it bought quinine that wasn't quinine and it got upset. So, in 1848, with the troops attacking Mexico City, their quinine didn't work like it was

supposed to, they said what's in here, it wasn't quinine, it was something else, I don't know what it was.

They said that's terrible, terrible, terrible, and so we needed to find a way to make sure that when something was labeled quinine, it really was indeed quinine. That was the first shot out of the cannon.

We finally had the Food and Drug Act of 1906, which really just said that if you are going to sell something and call it a drug, and name it, it ought to be what you call it. Right about that time we got into the concept of misbranding, which was putting something in something and calling it something that it wasn't, and that is basically what misbranding is.

We have a lot of meetings for misbranding now, but the bottom line is that it is not what it is supposed to have been.

The Agency wasn't really founded then, but the government said that if we wanted to take action against the company that misbranded a drug,

that it was incumbent upon the government to prove that the drug was indeed not what it said it was, and that there was intent to defraud. If you do that to the government, we can't enforce any quality on anybody, because we don't have any information to use for it.

But I want you to remember that concept that came about in the early 1900s, because when we get to the end of the 1900s, we have another law that brought us right back to that place.

So, 1938, we killed a bunch of kids in the New York City area with antifreeze as a sweetening agent in a sulfa drug preparation. That was the end of a company's reputation, and well it should have been, and everybody was in an uproar, so we now have a new regulation. You will notice the trend here - disaster, new regulation, disaster, new regulation. It's kind of a recurring theme.

So, we know said, okay, it has to be what it says it is, it has to contain what it says it contains, and it has to be safe, but it doesn't have to work.

Homeopathic remedies are exactly that. They are 1 to 100 dilutions of something done 1,000 times. You end up with a bottle of water, which they claim contains the essence of the power of whatever drug was in the first bottle of 1,000 dilutions before. All right. So, we can claim it works, and it contains a diluted, diluted, diluted, fine, that is what it really contains. You can't find a molecule because you have diluted more than Avargordo's number, so we have products on the market.

By the way, the Food, Drug, and Cosmetic Act says specifically that drugs are things that are contained in the homeopathic pharmacopeia, which means that they are precluded from acting against products that are in the homeopathic pharmacopeia even though we know they don't work.

We are still working with things that are just safe, but at least they are branded right, you know. Nowadays we have people who claim that water solves medical conditions. What the heck, you know, 1938, that would have worked, put a label on

water, say, if you will bottle water and pay for it at a rate higher than you pay for gasoline, then, it is better for you than the water you get for free out of the tap, and you will do better.

Well, I don't know, I wonder about things like that. I have a problem my students always complain about. I have one of those minds that kind of wanders, and so I do that.

Let's get back to misspelled words and regulation. So, in 1951, two pharmacists got together, a guy named Carl Durham and a guy named Hubert Horatio Humphrey--I love his name. They were pharmacists. One was in Congress and one was in the Senate. Hubert came from Minnesota. He ultimately became vice president, ran for president, didn't make it.

I often wonder what would happen if the president of the United States was really a physician or a pharmacist, a health care worker, what difference that would make in their approach to the health care problems.

So, they got together and they said, you

know, there is a lot of drugs out there that are pretty dangerous, that the average person really can't understand, and maybe we ought to have somebody help them figure out what to take, so they established two criteria, prescription drugs and over-the-counter drugs. We still, by the way, don't have to have them work. You know, God forbid, they actually should work.

We are a unique country among the developed nations of the world. We only have two categories of drugs. Most of them have many more categories of different levels, and, in fact, I like the Australian system. They are listed in the group of things they call poisons, so we clearly know where they belong, right? They are the poison list.

In 1962, we finally got around to hoping that we could figure out that the drugs were both safe and effective, so in 1962, we said, okay, new drugs have to be safe and effective. The Agency was kind of curious. It said, but you can't tell people that this is an approved drug, because that

gives you a marketing advantage over the drugs that haven't been approved by us, and then we don't know are effective. Hmm, that's interesting.

Then, Congress, in its infinite wisdom, jumped right in there with DSHEA, and DSHEA says that if you aren't really a drug, but kind of imply that you are a drug, then, you can go back to the 1906 regulation which says that it only has to be what it says it is, and it doesn't have to be proven to be safe or effective, and if there is any problems with it, the Agency has to compile the data before they can make you take it off the market. I just love that, you know, retrograde regulation, I just wonder about the wisdom of that. I am sure it has to do with the need that the public has for unsubstantiated claimed herbal remedies.

All right. Here is where we really get to where the rubber meets the road, and that is the cost of drugs. I grew up in a pharmacy family. My father was a pharmacist, my uncle was a pharmacist, I became a pharmacist because I didn't know

anything else.

I grew up in a drugstore, and when I was at a young age, I worked in my father's drugstore as a soda jerk. Some people think that I have never gotten over the second half of that.

But in those days, the average cost of drugs that my father filled--he has a wonderful ledger, handwritten in ink pen where he wrote down the name of the patient, the prescription, the physician, and then the cost--and if you look at it, you will find that the average charge to his patient was $1.75.

I asked him one day, being a nosy teenager, how do we make money to live on at the store here, and he says, "Well, I charge $1.75, but it costs me about 25 cents of goods." So, I said I thought that was pretty good.

Of course, nowadays, the average charge of a prescription can be in the $50 or $60 range, and the pharmacy gets $3.50. There has been a shift here somewhere.

At that time, Tetracycline came out. It

was about 50 cents a capsule. The price of Tetracycline has gone down dramatically, but we keep bringing out new drugs, and I think each time we bring out a new drug, we say what was the price that we charged for the last new drug, and we multiply by 1.5.

You also understand that there is absolutely no relationship between the charge for the drug and the cost of actually manufacturing it, and that they factor in all of the other costs to maintain the corporate entity that creates new drugs. So, they need to have this huge inflow of money in order to float all of the research and the marketing, and all the other efforts that go on, and so that there is some disconnect.

Waxman and Hatch got together. We recognized back in the 1980s that the cost of health care was going up quickly. Uwe Reinhardt has a wonderful graph that he puts up, a Princeton economist, that shows the gross national product and its rate of increase and the cost of health care and its rate of increase, and then he predicts

some date in the future where the two will meet.

Then, he has a cartoon where he has two physicians lying in beds in the hospital together, prescribing for each other, and he said that is going to be the entire productivity of the United States is going to be this.

So, we know that there is a disaster in the future and what are we going to do about it, and we have a culture in the United States where we don't regulate the price of drugs. We are again unique. Very few developed countries have that compunction. So, we try to regulate it through competition.

So, the Waxman-Hatch Act or the Hatch-Waxman Act, depending on whether you are a Republican or a Democrat, came into being, and it was a compromise that was supposed to benefit the innovator companies by ensuring them a reasonable patent extension or exclusivity time frame in order to recoup the investment to bring the new drug to the market, and established rules and regulations for the development of generic drugs.

It seems to work in some areas and we hope for the best. However, it is not going to be the end of the issue, and if we start to make projections out in the future, we are going to have to do more than that in terms of cost, but it was the first time that the FDA was an active participant in controlling costs.

I think I see that as something going forward. We have a problem, of course, with other issues associated with cost, and, of course, here comes re-importation, and we are going to get into that in a little bit, but I don't want to beat a dead horse.

My wife is Canadian and my inlaws are in Canada, and they see the U.S. news come across that says that Canadian drugs are bad for American citizens, and they say, oh, and they call their son-in-law, the expert, and they say, "What's wrong with Canadian drugs?" Of course, i am hard pressed to say anything about it, because there is nothing wrong with Canadian drugs. So, that makes an interesting argument. I think we can go down that

road as long as we want.

I think the next level of regulation is going to be the line on top. People are going to want information that shows that the next new drug is not only safe and effective, but better. I don't know how long it is going to take for Congress to do that, but that is what is coming.

We have a history of producing lots of drugs that might be different, but not necessarily an improvement, where are we going to go, and I think both the industry and the Agency should be prepared to think about how they would handle that situation.

Remember that we are trying to regulate according to best science, and sometimes we lose track of best science. There are some classic equations that we use that we depend upon to help us decide what is good science. One is the Noyes-Whitney expression. The Noyes-Whitney expression describes dissolution profile, and it was developed by these gentlemen using a very interesting standard material. It was a fused

cylinder of material.

So, their apparatus and how they did it were standardized based on one solid hunk of an individual chemical in the cylindrical form, so they could accurately determine the area exposed to the fluid and therefore, from it, determine all of the equations. Nowadays we use a standardized compressed tablet. I would argue that the dissolution apparatus is probably less variable than an individual tablet coming off a tablet run.

If you wanted to standardize an apparatus, you ought to standardize it with something which is less variable than the apparatus you are standardizing. I wonder about that. I guess we could ask our colleagues down the street what they think about that, but let's go back to the basic science and figure out what is going on.

The other one I like to talk about occasionally is Arrhenius. Arrhenius developed a relationship between temperature and rate of reaction that was developed for reactions that happened in dilute solutions.

We apply them, same rules, too, tablets, ointments, creams, and lotions. We put things aside for three months at elevated temperature, and we say this is going to predict what is going on in two years. We will give you two years, just send us the real data later. I would argue that if we went through the data that the Agency has, that we would be hard pressed to get a correlation coefficient much over 0.3 for that data.

The other thing is what is the rule and regulation. When a rule or regulation gets out there and purports to be doing something, and it doesn't, it makes you wonder. We have a regulation that says you have to do accelerated stability at 40 degrees and 75 percent relative humidity, but you can take the humidity and temperature chamber and you can put in it a tablet container that is sealed with a descant in it and do the study.

That is kind of like saying let's see how fast ice cream can melt in the kitchen, but you are allowed to put it in the freezer. I wonder, you know, I just wonder. I am just kind of curious

about those kinds of things. You sit around in an academic office, you are a tenured full professor, what are they going to do. You wonder about those things.

I think that there is going to be a lot of international regulation. I think that we are at the stage where the companies are truly international. The largest provider of generic drugs in the United States is in Tel Aviv. Most of the big developmental innovator companies are really housed everywhere.

In fact, the numbers of workers at pharmaceutical plants in the world has shifted from the United States out. If that is true, then, we really have to have cooperative control on quality. I am sure that England and Germany and France want the same high quality of drugs as we do, as the Canadian Health Protection Branch insists that they do.

So, we need to go in the direction of what is truly a harmonized or internationalized regulation of quality. We need to somehow control

the cost to the consumer, and if we don't find a way to do that, it will be imposed on us.

One of the problems I have with all of this is that drug costs to consumer seems to make the news way more than the cost of a bed in the hospital. Now, I will just ask you, how much does it cost to be in a hospital bed. Does anyone know? No, but you sure know how much it costs for a bottle of Viagra--oh, excuse me.

DR. SINGPURWALLA: I don't.

DR. KIBBE: Oh, there is a man with confidence.

[Laughter.]

DR. KIBBE: The reason is that most of us in the public are covered by some insurance plan that covers the cost of the hospital bed, but we aren't covered by drugs, and drugs represent 8 to 10 percent of the total cost of health care in the United States, and if you look at it, it is much cheaper to give reasonably expensive drugs to patients than to put them in a hospital. But the patients don't pay for it out of pocket.

I wonder why the huge lobbying efforts of the pharmaceutical company isn't applied to getting drugs covered by Medicare and Medicaid instead of anything else. If they could ever do that, they could forget about the arguments in the newspaper about the cost of drugs.

I am sure there is lots of economic issues associated with that.

The last three things I have are continuous quality improvement, PAT, and federally-funded efficacy testing. I don't know whether we are going to get the right to demand that you do an efficacy test against seven or eight of your competitors in order to get approval, but I think that the world deserves a chance to look at what is those relative efficacies in an abstract or at least impartial way.

PAT has been fun for me. I think it's a wonderful initiative, it has its own journal now, those of you who are interested in it. It has got a forward written by--oh, my heavens--Ajaz. It has some beautiful pictures in here.

I went through it immediately and wanted to see if I knew anybody that actually was involved in PAT, and there is a whole bunch of really pretty pictures of all sorts of people that were actually on the committee with it, if anybody is interested in it. I thought that was pretty neat.

I think that there are things in the horizon that really threaten the way we do business both at the industrial level and at the regulatory level. One of them is the development of nanotechnology and computational power.

We are looking forward to a singularity in computational power, a point beyond which we cannot predict or even understand the future. In approximately 2014 or 15, the computer on your desk will have not only digital computational power, but parallel processing, and will be able to think better than you can. We will be able to process data, come up with new ideas, and, in fact, at some point in time, it will be the most intelligent being on the planet, and we humans will relegate ourselves to second place.

When that happens, what do we do about health care? And let's look at nanobots and what they can do. If aging is truly a degradation of the DNA strand within people, if we can inject nanobots who know how to count DNA strands and repair them, how are we going to age?

If we have the capacity to scan individual molecules and relationship in the neural net, can we then scan down a person's entire knowledge base and personality, and shift it from a carbon-based, short term, to a silicon-based, long term holding facility?

How many of us would be willing at the ends of our days to become virtual us in a virtual environment?

Where are we going? Challenges to the FDA. In our experience over the last several millennium, an ever- increasing rate of new technological development. It was 20,000 years from the time we developed hand-held rock until we actually made a bow and arrow with a processed rock, and the rate at which we develop things now

is astronomical.

We need to have improved productivity in the industry, but that needs to be related to an improvement in the cost of goods sold to the American public, and the Agency needs to maintain public confidence. It needs to not say things that are clearly difficult to defend in the public environment. It needs to be responsive to the public needs and realistic, so that the public understands the expectations of drugs.

If there was any advertising that the Agency could do, that I think would help in the long run, it is to get the American public to understand that drugs are not safe, that they can be used safely.

The American public has an unrealistic expectation for their medications and an unrealistic expectation of how they should feel as they go through life, and they expect that these little pills will do it for them, and it won't, and we need to get them to stop thinking that way.

We need to maintain and improve

international cooperation in both regulation and harmonization, and we need to, in the final analysis, decriminalize Grandma. When she crosses the border to pick up drugs, she needs to understand that we don't think that she is committing a heinous crime against society, that we understand that the economics are driving her to it, and we need to find a way of making it happen for her, so that she can get the drugs she needs at the price she can afford.

Does anybody have any questions?

[Applause.]

DR. KIBBE: Thank you, Dr. Kibbe, for that exhilarating presentation. I am sorry, I just love those kinds of things.

Now, we are going to get into some serious stuff here, because Ajaz is going to get up to the podium.

DR. HUSSAIN: Could we just take a break now and then start after the break?

DR. KIBBE: I am still fired up, you know, whatever you want to do. You know the energy level

after making a presentation. I really want to complain about the lack of a soapbox. I asked for a soapbox up there because I knew I was going to get on my soapbox.

Ajaz wants to take a break. Let's try to get back and get back to work at two minutes to 10:00.

[Recess.]

DR. KIBBE: We have comments on my talk that some members would like to make, and then I am going to be more than happy to add to my talk a few other issues, so we might have a lot of fun today.

As is the tradition with this year's committee, Nozer has a comment.

DR. SINGPURWALLA: I don't have a comment, I have a question for you. The question is what would your reaction be to the idea of nationalizing the drug industry?

DR. KIBBE: That is a wonderful question and I think the answer to it resides with our colleagues over there. I know that if they ever did that, I would volunteer to be drug czar. There

are a couple of issues that I didn't hit on in my thing. One of them is direct-to-consumer advertising. I think the issue of why the public has the misconception that drugs are not safe can be tied directly to direct-to-consumer advertising.

Many years ago, in my one opportunity to appear on the Today Show, I was interviewed by Debra Norville on the topic, and I was debating an industry representative, and I said that it would completely change the dynamics of prescribing and using of drugs in the United States, and I think it has.

Two days ago, I was sitting at home watching TV, and for an hour and a half, every single ad on TV, every single ad was for a prescription drug, and it just has to have a dramatic effect on the way patients interact with their physician and how they get health care. I think it was a mistake, but we can comment on that, too.

Does anybody want to throw a few cents' worth in while we are prognosticating?

MR. CLARK: You mentioned something about E.R. Squibb challenging the world to meet his efficiency in his products that he manufactured. I was just trying to point out that while he challenged the world, that challenge could prove fatal today, because today, Mr. Squibb or Dr. Squibb would be required to freeze his manufacturing technique, whatever it may have been, and that while his challengers came in with new techniques, he would be burdened with an approval process that would slow down his ability to compete, and we should be able to create a regulatory environment that protects the public as it still encourages innovation, and not just encourages the innovation for innovation's sake, but encourages applying it to the products and to improve the entire environment.

DR. KIBBE: Clearly, he couldn't do what he did then now, because the Federal Government is in his business now.

MR. CLARK: Exactly.

DR. KIBBE: And that has happened after

World War II. Before World War II, the Federal Government stayed out of everybody's business, and that is a dramatic change in the way we do business in the United States.

We need to get to the desired state--I recommend Pennsylvania, far less hurricanes--the desired state, however, is going to be defined by Ajaz.

The "Desired State" of Science and Risk-based Regulatory Policies

DR. HUSSAIN: I will do it from here. In a sense, what we wanted to do, sort of build on the Manufacturing Committee discussion that was reported quite elaborately by Judy Boehlert, the chair of that committee, but to sort of now do a gap analysis, what we see as gaps between the current state and the desired state from an internal FDA perspective, what are the challenges we face internally, and get your feedback on that.

So, what we have are three presentations, one, Helen will sort of look at the organizational issues, I will try to identify some of the

scientific gaps, and Jon will identify some of the policy gaps and how we intend to sort of fill those gaps.

If you could sort of give us feedback on are we missing in our gap analysis, it is a preliminary gap analysis right now, and then how we proceed, and then this will be followed by discussions and presentations by PhRMA and GPhA perspective on how they see the progress we have made and some of the challenges that remain.

So, that is the discussion for this morning.

DR. KIBBE: That means you are passing the ball to Helen.

DR. HUSSAIN: Yes.

DR. KIBBE: Let's see how you follow my act.

Organizational Gap Analysis

MS. WINKLE: Believe me, in 100 years, not only could I not only follow your act, I wouldn't know where to begin, and my topic is so boring anyway.

I am going to talk about organizational gap in the Agency right now as far as the desired state is concerned, and as Ajaz said, this is sort of a follow-up to some of the things we talked about at the Manufacturing Subcommittee, and I think it is really important that we look at these gaps and talk more about them, and sort of discuss how we can possibly fill some of them.

I have some ideas on filling on some of them, but I think there is a lot more that we will need.

DR. KIBBE: There appears to be a gap in the computational problem, too.

[Pause.]

DR. KIBBE: We are passing around a transportation note for people who need help to get to the airport.

MS. WINKLE: Is everybody leaving now? Gosh, you could at least have given me a chance.

[Laughter.]

MS. WINKLE: As I said, I am going to talk about the organizational gaps and reaching the

desired state, and I wanted to start off with, just a second, showing you the organizational chart of OPS, because I think as I talk about organizational gaps, you need to know a little bit about what the organization looks like, and I think you have a good idea, but I just wanted to point out we do have four offices.

You actually heard from all four of those offices yesterday, but you say, in yellow, where the CMC is done in all four offices, so almost every part of the organization in some way is affected by the changes that are being made by the new paradigm and what we are trying to accomplish with the desired gap, which complicates the issues somewhat.

It is very important as we look at the organizational gaps that it is multi-dimensional, it goes across all of the organization. It is between organizations and it is within organizations. There is lots of gaps here and we need to look at all of these gaps and figure out how we are going to handle them.

It is outside of OPS and other parts of CDER. We really do a lot of work with products with devices with CBER, so we need to be sure that those gaps are closed as we move forward in trying to accomplish the desired state.

So, basically, what I am going to be talking about here is what we need to consider and resolve in our process or processes before we can adequately implement regulatory direction and support through applications process and review of what we are calling the desired state.

I also want to point out as I talk, and you will see this a lot, that the organizational gaps that I am going to point out really intersect with the science gaps that Ajaz is going to talk about and the policy gaps that Jon is going to talk about, and you probably can't really address any of these separately although that is what we are making an attempt to do here. But again as I go through the organizational gaps, you will see a lot of the intersections.

What constitutes the gap in OPS and what

are actually the process issues for implementing the desired state, and how we will review at different levels? This is really some of what we need to talk about.

One of the big problems here is the appropriate utilization and focus of available resources. I am reading it wrong. This is why I am having problems. It is the resources. We have a lot of human resources. You have already heard some of the issues that we have had with how to use our best resources and how to focus those resources on those issues that are most important. So, that is really one of the things that we have as part of the gap.

We are not always focused on those issues which are the most important, and we don't always have the science expertise available to focus on the gaps or focus on the issues correctly. So, this is a big gap that we have across the entire organization.

There is a difference in products and regulatory requirements and review processes. We

are regulating ANDAs, NDAs, and BLAs, and BLAs even fall under a different act than the ANDAs and the NDAs. So, there are some complications and some gaps there that we are going to have to look at and determine how best to handle.

The organizational structure, the way it is set up really creates a really large gap in how we are going to move forward.

I think we have made it clear in the past that in ONDC, I know Moheb has talked about this at different times, Dr. Nasr has talked about this at different times, that we have chemists from the Office of New Drug Chemistry that are located in the different clinical divisions, so that we lack consistency in how they make decisions often, because it is done outside of the whole chemistry structure, so to speak. It is done within the Clinical Division, and we also lack the flexibility of being able to use our staff and to utilize the science and the staff because of these collocations.

Actually, we have chemists in 18 different

teams across the Clinical Divisions, and they very rarely interact with each other, so it really causes a lot of complications in how we do our work, and it will cause even more complications when we get into the new paradigm.

I think one of the main gaps is that we are very process driven, not science driven. This goes back to the earlier comment by Dr. Kibbe. We are regulating a science industry. It is a science industry that we are regulating through process.

Some of the things that contribute to this is PDUFA in generic drugs, first in, first reviewed. We have a tiered approach to our reviews. We have heavy backlogs. I think that Gary has made that point several times to this committee. The workloads are big, the backlogs are big. So, that is really driving us, too, to focus more on process than science. So, this is causing us to really have to rethink how we want to do things.

Part of what is adding to that workload and to the backlog is that we get too many

supplements. We require supplements on little changes that really have no significance in the manufacturing process.

Also, part of the gap is the interaction with inspection. We have a lack of appropriate reviewer involvement, and we get no feedback. We do not get copies of 483s. Once they have been in to the industry with the observations, we don't even have any correspondence in most cases with the inspection people on things that they find when they go out on inspections.

So, how you are supposed to really have knowledge about the products that you are reviewing in the future or where you can use that knowledge that has been gathered and incorporate that into your thinking about reviews and products, you can't do, so that really creates a lot of gaps.

One of the things that is going to create a gap in the future is the possibility of having a two-tiered system. As we talk about the desired state, as we talk about the things that are required under the desired state, we don't have

regulations that are going to require manufacturers to submit pharmaceutical development information. We don't have regulations that are going to require them to do this thing or that thing, and in some places, I am not even sure we have the carrot to encourage them to do that.

So, you are going to have some companies that are naturally going to submit this stuff, or naturally going to move toward PAT and toward other aspects of improving on their manufacture, but you are going to have companies that don't, so what we are looking at is the possibility of having a two-tiered system which is going to create a gap even within one reviewer.

He is going to have to be able to look at both tiers and make decisions, and this is going to complicate issues a lot when we move ahead.

We use guidances to accomplish consistency, and those guidances are sometimes very prescriptive, and this adds to the whole gap, and also not only are we using guidances for consistency, they are also up for interpretation.

Unless they are prescriptive, they are interpreted differently by different people, so obviously, we have some concerns about this.

Organizational components are too reactive, and not proactive. Now, this is caused by workload, and the workload continues to perpetuate the problem.

You have to be reactive because you have so much work piled up in your In box that that is what you have to focus on, and it is very hard to be creative and innovative and think about those issues and problems that you are going to have down the road, think about, as Dr. Kibbe was talking, new therapeutics that are coming along or new novel delivery systems or different things like that, too busy moving the freight from day to day.

Use of available scientific expertise and scientific collaboration. Often within especially in ONDC, because they are broken up according to the clinical divisions, you may not have the necessary scientific expertise to look at an issue, to look at a problem, to know really what the right

direction is for making a decision on a product.

Also, we do not go out and use a lot of scientific collaboration. I mean we have a lot of SGEs, we have several in this room that are helping us on different scientific issues of a broader nature, but we could be taking advantage of some of those and calling and getting more information in the future.

There is a challenge in focusing on the appropriate questions or what are the right questions. Reviewers have a tendency--and this is not any kind of negative against reviewers--but they do have a tendency to look at all the data that is provided, and we have not focused down on what the appropriate data is, and, therefore, the appropriate questions that we need to have answered.

We have a lack of utilization of appropriate tools. We could be using statistics more, all of us, to get better answers to some of the questions that we have around review. There are other tools, as well, that we could be using

that we are not. One of the big areas I think that causes a gap is the lack of communication between disciplines, but I do want to add to this, there is also a lack of communication between organizations or components of the organization, and this is one of the things that we need to focus on to help close the gap.

So, I did take a look at what we had done so far for closing the gap, because I think it is important to emphasize some of the stuff, because we do realize that we have some big gaps here.

I do want to upfront say, though, that these are not all of things that we need to do. I know that there is a lot more down the road that is going to come along, and I am really looking for advice from the Advisory Committee as to some of the things that we need to be thinking more carefully about, or make suggestions for some of the things that we could be doing to help close this organizational gap.

One of the things we have been doing is making some structural changes in the organization

In the Office of New Drug Chemistry, which Judy talked about yesterday for the Manufacturing Subcommittee, we are reorganizing the Office of New Drug Chemistry. We are actually doing away with the collocation and making one Office of Chemistry when we move to White Oak.

We feel that this is going to give us a lot of consistency or at least more consistency, and give us the opportunity to have more flexibility as to how we look at the review process. We feel that this is going to have some real advantages to us.

We are also, in our Office of Generic Drugs, we have set up a third division for doing chemistry. The workload is so heavy in the office that we felt like if we had more divisions where we could spend more time and focus more on some of the issues, that we could help in some of the gap problems, having reviewers on inspections or as consultants to inspection, so have complete knowledge on products and the results of inspections.

This is something that we have been working on. We have been working with our Office of Compliance and with our field component. We feel like we would like to have reviewers on inspection. We think it is very important for them to go out and provide some of the scientific knowledge to the inspectors as the inspections are being done, but I don't think that part of the question even came up yesterday on resources to do this.

This is a resource issue. You are taking people away from their desk to go and--we have already talked about the workload being high--taking people away from the desk to go out on inspections and spend time away from their desks, but also this is costly, and like it or not, we are not flush with money, so we won't be able to do this in every inspection.

But I do think it is important that before the inspections are done, even though the reviewers can't go out, that they provide consultation to the inspectors and talk about some of the issues that

they have seen in the reviews of these particular companies and give them some advice on what they may want to focus on more in the inspections.

One of the big things that is really necessary, in my mind, to closing the gaps, and again this sort of goes across the whole concept of the science gap and the guidance gap, and our policy gap, as well, is that we have a lot of questions we still need to answer and address.

This is only a few of them, but I think there is a lot of things that we have not come to grips with on manufacturing science and how that is going to affect our review and what our review process is going to be to handle these things in the future - things like quality overall summaries.

Dr. Nasr talks about incorporating this into the process of ONDC. We have not come to any conclusions on this. We are still in the proposal stage. We need to decide, if this is the direction we want to go, what is the benefit of it to us, to the industry, and what we really need to see in that QOS. So, that is a question that we need to

look at.

What we need in the way of pharmaceutical development information. There is a lot of information that these companies have in the pharmaceutical development arena, and do we want all of that information. If we get that information, what are we supposed to look at, what would we focus on. We need to answer those questions, it is very important, before we start asking for this information.

We have to have addressed that before, I think, companies are going to feel comfortable in providing it. I think many companies see this as just more information they are sending us to look at and more questions they are going to get from us, so we really have to develop our processes.

We also need to look at things like how industry will determine critical attributes, so as we look toward the desired state, that we are able to regulate that and include those in our process, and we need to know in all these cases what we will do as far as reviewing these.

This is just a small part of the questions, I think, that we need to be addressing.

Also, as far as closing the gap, we need to have a better understanding of what constitutes the design space across all products, and once we have a good feel about that, or understand that, we need to know when notification to FDA is necessary for change in manufacturing.

We have not reached these conclusions yet, and we need to have working groups, whatever it takes, to really develop our own internal thinking on this and work with industry to make sure that the direction we are going is going to be useful to them.

We need to have a better understanding of what risk for a product is and develop a systematic risk approach to review processes. I keep seeing time and time again, people talk about risk management or risk processes, and stuff like that. I think when you talk about risk management, you are talking about something different for every person.

I mean what is in my mind, what is in everybody else's mind in this room could be entirely different, and we at the Agency need to narrow down as far as review is concerned, decide what that means, how we are going to use it, and have a very, very concise program for ensuring that we do look at this in a fair and equitable way.

Guidances. Again, Jon is going to talk about guidances, but it is really necessary for us to go back. This will help us close the gap, but we need to go back and look at our guidance. We have many guidances out there that are outdated, many guidances that are overly prescriptive, many guidances that don't fit into the new paradigm at all.

Jon is in the process, he and his staff, of going through the guidances, removing some, redoing some, and looking at what guidances we will need for the future in order to incorporate some of the changes.

Training. This goes to the question Mel asked, training, training, training is necessary

here. We have so much to train. We are doing some training, and I will talk about some of that, but I think it is really important and part of what we need to do to close the gap, is determine what really training our reviewers need and what training is necessary for the industry, and I don't think we have come to those conclusions yet.

We need to determine how we are going to work under a two-tiered system if, in fact, that is the direction that we go, and we need to have developed the processes for doing that. We need to develop an internal system for handling differences in Review Divisions.

I met a couple of months ago with PhRMA on a RAC Committee on a dialogue session, and this was one of the things that came up was the need for a dispute resolution process, some kind of mechanism where, when there are differences in review, that we are able to handle those decisions and get information out as to how these issues are resolved.

The last thing I have on here--and

actually, I wrote this slide before we even had some of the conversations yesterday--was what is really important is we need to have appropriate metrics for measuring things.

Today, in the review, we measure by what we accomplish, how many supplements we get. Well, let me tell you when you are measuring supplements, and that is an indication of how good you are doing your job, you are going to want more supplements.

We have got to really back off of the metrics that we currently have and look for those appropriate metrics to help close these gaps.

So, some of the current steps we have across OPS, we mentioned before that we are setting up a working group under the Manufacturing Subcommittee of the Advisory Committee to begin to address many of these questions that we have. We are also setting up some CRADAs to get some case studies to help us, too, in getting a better understanding of these issues and how we are going to handle them in our processes.

ICH, too, is going to be an important part

of helping us handle some of our organizational decisions especially Q8 as it looks at the desired state and implement some guidelines on it.

We are doing some workshops. We have a Workshop of Specification Setting and looking at how we need to have a mechanistic understanding of setting specifications in line with the direction that we are going.

That particular workshop is set up in March, but I will be upfront with the fact that I think there is still going to be issues that come out of that workshop where we are going to have to look more specifically at some of the specification areas and really dig deeper into them, so I really anticipate more workshops than this just in the area of specifications, but I think a number of workshops are on the horizon in order for us to be able to address many of these questions.

I actually think, too, one of the things that we are probably looking at having a workshop on is quality overall summaries. If that is the direction we want to go, I think we need input from

the industry and others, so that we have a better understanding of what we need for using that type of process and what it means to us in the industry when we do.

We already have some collaboration with academics. As I said, we are involved in several CRADAs or in the development of several CRADAs. I think these are going to be very helpful for us in getting a better understanding of some of the areas that we need to, or some of the questions we need to, answer, so that we can fill some of those gaps, and we have been doing some work with the Product Quality Research Institute.

As I already said, we have an internal review of our current guidances, which is very important to helping us have the appropriate guidances out there. We are developing a program for team interactions for inspections.

We are sort of basing this on how we have handled PAT and the team approach, and we are working with Compliance in the field to develop a better way of handling inspections and including

the Review folks in those inspections, and also a better way of getting the findings from those inspections.

Training for reviewers. We have already had a number of scientific seminars. We have started that, especially, OGD has one every six months or so, and those seminars have been very beneficial to our staff in helping us have a better understanding of where we need to go, but we need more seminars and we need, again, really a set training program for all of our reviewers.

We did form an OPS Coordinating Committee within the immediate office, and actually, Keith Webber and Gary Buehler are the chairs of that committee, and we will be looking at all the issues that come into OPS to try to ensure that we have consistency throughout all of OPS on handling these.

One of the other things that we are in the process, I think, that will help with the gap is finalizing the guidance on comparability protocol.

Also, in ONDC, as I said, we are really

changing the organizational structure, but much more than changing the organizational structure, we are changing from a review program to an assessment program, and that assessment program will focus on quality attributes of the manufacturing including chemistry, pharmaceutical formulation, and the manufacturing process.

So, the significant thing here is that we will be looking at much more the chemistry, the CMC, and that is where the assessment program is focused.

We have the proposed QOS. We have also implemented a team approach. We are establishing a peer review process. We have already done this on a limited basis to provide more scientific input to our scientists in their review processes, and helping everyone have a better understanding and sharing the knowledge that they learn from the reviews.

We are implementing a Quality Systems approach. One of the things, too, that ONDC is doing, is they are developing a mock NDA under the

new paradigm, under the desired state paradigm, so that they will have a better feel for some of the questions and issues that can come up, and they are looking at reducing supplement requirements.

OGD has reorganized, as well. As I mentioned, they have an additional Chemistry Division. They are looking at changes in the supplement review and evaluation to determine if some of the supplements can be eliminated.

They have also taken on the team approach on some applications, so that they have better utilization of scientific expertise and ensure consistency across similar product areas, and they are also looking at efficiencies in review to eliminate redundant or non-essential review activities. So, they are very much involved, too, in some of the things that we need to be focused on in order to eliminate the gap.

OBP, which is, of course, our newest review organization, is looking at supplement requirements to determine where we can eliminate or reduce supplements.

Some additional steps. I think we need to involve stakeholders in the review of guidances. Maybe under the Manufacturing Subcommittee we need a group that looks at some of the guidances. I don't know how we need to do this, but I think it is a step we need to do.

We need to determine how to handle the two-tiered approach, if we do it at all. I have mentioned this before, and I think it is going to be important to involve industry and others in doing that.

We need to have external workshops, develop a dispute resolution process. One of the things, too, besides looking at regular GMP inspections, we really need to look at better ways to handle pre-approval inspection process.

I would really like to see reviewers more involved in making some of the decisions on whether to do pre-approval inspections and to set better criteria for getting those done plus participate on the inspections if we feel they are necessary, and develop appropriate metrics. These are things we

haven't started on, but are obviously necessary, and I am sure there is others.

Just to finish up, observations and conclusions. I think we need to continue to address and analyze the organizational gap issues. I think they are going to be really important to us, to have determined what they are and to resolve how we are going to handle them in the future in order to move in the direction that we need to do to be able to regulate under the desired state.

One of the things I think that is very important that we need to think about is culture. When I talk about culture, I am talking about the culture within FDA, and I am talking about the culture outside of FDA.

There are a lot of changes that need to be here. I realize that the culture is always a different area of thing to handle. I thought Jerry's example was an excellent example of how the culture is a problem in some of the things that we are trying to do, and this is one of the things that we have got to manage and figure out how best

to handle.

All of this, all of this, the changes in the organizational gap will take time, and we need to be dedicating the time to make it happen.

Also, as I said, a lot of this depends on resolving some of the science gaps that we have. We need to include stakeholders in making some of the decisions and developing some of the procedures. We need to work closely, I think, with the stakeholders or we are really not going to have the answers that we need.

The training of reviewers is important, and the thing I think that is going to be something that we have got to be open to is that as we move forward, we are going to see other gaps that we haven't anticipated, and we are going to have to be ready to fill those.

That is all I have. Thank you.

DR. KIBBE: Thank you, Helen.

Should we take questions or you want to move to the--

MS. WINKLE: Let's go through all of it,

yes.

DR. KIBBE: I will hold my really tough and incisive questions until later.

Scientific Gap Analysis

DR. HUSSAIN: Last night I had a phone call and I couldn't answer that, but this morning, at 7:00, I had another phone call from a company which recently got an approval for an inhalation product, and they were ecstatic. They had submitted a complete development pharmaceutics report, and that process went extremely well. This was a one-cycle review approval for an important product including all the development report.

So, I think that is a wonderful example that shows ONDC has already moved and things are moving in this direction already. We probably will make a case study out of it, and so forth.

Anyway, I would like to sort of focus on the scientific gaps. I will use some background information. I know a number of members on this committee who are new, so I thought I will spend some starting with the basics.

I think, as Dr. Woodcock had come to the Manufacturing Committee, her articulation of what is quality has really come to almost fruition, and she is publishing this article soon. The definition of quality is fundamental as we move forward, and there are some challenges as we move forward.

Good pharmaceutical quality essentially means an acceptably low risk of failing to achieve the desired clinical attributes. That is the goal of achieving quality.

The challenge has always been, and you heard many of the discussions yesterday, saying the weakest link--and the weakest link is what we have to strengthen and address--how do we link measurements and risk?

I think what we believe quality by design approach that we are developing under ICH Q8 is a way to help that. It is a multivariate model. It is characterized during development. You have to think about, when you think about quality by design, the clinical is a confirmation of that.

That is the fundamental aspect that I think is going to be a significant challenge in how we achieve that.

At the same time, you have to remember that development is only one part of it. You essentially have to make sure you have a quality system.

The final link between product and customer-driven quality attributes really means you have a good quality system for manufacture that brought us consistently also, that requires integrated product and process knowledge on an ongoing basis, because you don't stop learning at the time of approval. In fact, you learn quite significantly after manufacturing status.

You have to assure ongoing control, and you have to enable continuous improvement.

In summary, I think Dr. Woodcock articulated this at our ONDC scientific rounds on October 6th. The future definition of quality should be probabilistic in nature. That is the fundamental aspect, and we are not there yet.

Science management, risk management, and quality management are critical aspects, and I think we really would like to be leaders in this, and I personally believe that we are.

But let me take a look backwards from beginning with the end in mind. Since we started the PAT Initiative, the cGMP Initiative, our focus has been on looking at the entire system, and we have been looking backwards from a manufacturing end to the entire discovery development product, and it is what do we learn from that.

But before you look, before you measure, it is always good to make sure your measurement system is good, so you get your eyes checked. That is the symbol there.

The reason I was so sensitive to that is I think the dissolution variability from a manufacturing end, we really fully appreciate it when we are putting that white paper together, that today, companies don't have the ability to document lower variability than that of the calibrated tablet, and which is made with the conventional

method, and so forth. So, that was I think a stark reality that a lot of us fully understood during this process. Art mentioned that, and so forth.

So, what are the challenges here in the sense the challenge is organizational communication, and knowledge sharing and information sharing. If you work in silos, the boundaries between organization, which I call interface, the quality of the interface between functional unit, that means the effectiveness and efficiency of the process, the interface can be handoffs between functions, and often is in need for better coordination, and that is what we learned through our GMP Initiative.

The rapid and broad movement of information and knowledge sharing is necessary for process optimization between organizations, within any organization itself, so we have to move from technology transfer to knowledge transfer.

But just toward the stage, reliability is a phrase that we often don't use in pharmaceuticals, but reliability has a very

distinct body of information, body of knowledge associated with that.

So, if you look at this figure, you have performance, you have life, shelf life, and you have a desired specification on both sides, on the performance.

The first, Figure A is good performance, but poor reliability because the performance changes significantly over time, and the variability of the spec changes, too.

The second one is good performance and good reliability over the life.

The third is poor performance below spec.

So, I think the key is when we think about performance, we are thinking about performance of the shelf life, the bioavailability, and so forth, remaining unchanged throughout the shelf life. Just to keep that in mind.

In the current state, today, chemistry, manufacturing, controls, design information available in applications is limited and varied. Our reviewers have a high degree of uncertainty

with respect to what is critical and what sort of process controls are necessary.

Our reviewers have significant doubt on the level of process validation and process understanding. So, they have no option but to focus on in-process and product testing. So, in the pharmaceutical manufacturing from an engineering sense, testing is control, but in an engineering sense, control is very different. It is a dynamic method. We don't do that.

Risk coverage post-approval is a challenge, and supplements are a means for risk mitigation. That is the way we have approached it.

Traditional use of market standards--these are the pharmacopeial standards--as release tests are not effective for process understanding and continuous improvement. In fact, by definition, if you have attribute data or so-called zero tolerance, continuous improvement is impossible by definition. That is the definition in QS 9000, because we can only have continuous improvement when the product is already in spec.

If you have zero tolerance criteria, by definition, the product is not in spec. So, that is the fundamental thing. Also, we understood and wrote about that in our Manufacturing Science white paper.

We have variable test methods for physical characteristics, less than optimal systems perspective and approach, low efficiency and high cost of drug development and manufacturing, and continuous improvement is difficult, I would dare to say not possible.

So, the success of the cGMP Initiative was to get a consensus desired state statement, so I am not using the exact words that we developed. They are modified and the desired state statements adopted by ICH, these are the ones. Product quality and performance are achieved and assured by design of effective and efficient manufacturing processes.

Since we are looking back from the manufacturing side, manufacturing goals are kept first.

Product specifications based on

mechanistic understanding of how formulation and process factors impact product performance, and an ability to effect continuous improvement and continuous "real time" assurance of quality.

Now, let's start looking at this in the sense what are the gaps and how do you fill those gaps.

Information and knowledge for regulatory assessment and decision process based on the desired state is information related to quality and performance and how the design impacts that. So, we need to know impact of formulation and process factors on performance.

We need information to judge and develop specifications based on mechanistic understanding. We need information to evaluate and facilitate continuous improvement, and continuous "real time" assurance of quality.

The focus is on design, and if you are a formulator, especially one trained a few years ago, or if you have been in the design business, this is simply logical extension, so this is nothing new

about this, but if you are not, then, you have to think differently the design process.

Design is about doing things consciously, and not because they have always been done in a certain way. It is about comparing alternatives to select the best possible solution. It is about exploring and experimenting in a structured way. So, that is what design vocabulary brings to us.

So, in the context of drug product development, design is about doing things consciously, so you start with the intended use. That is the fundamental issue. You cannot forget the clinical use of the product that you are designing. That includes route of administration, patient population, and all other things that impact on the intended use.

That intended use defines for you what the product design should be. You have options to select, and you select a product design. That design leads you to design specifications, and those design specifications define the manufacturing process and its control necessary to

develop those design specifications back to deliver the intended use.

So, you have product performance, design specification that reliably and consistently deliver the therapeutic objective, and you have manufacturing capability, ability to reliably and consistently deliver the target for a design. This is straightforward, logical, no rocket science, and we have been making and doing this for 100 years.

So, that was the basis that we said we will develop the ICH Q8, and ICH Q8 document, which will go to Step 2 in Yokohama, I am confident about that, will essentially bring this type of information.

It will not deal with the drug substance manufacturing part of it, but it will start with drug substance characterization.

So, it will bring in characterization of components of drug product. It will bring in aspects of manufacturing compatibility, and so forth. Much of this information is sort of missing or varied in the current submission, and we are

hoping, although the sections in CTD-Q (P2) are not ideal, we have to live with that because that is how everything goes in green, we felt that the sections provide enough room for bringing all the information to bear on that.

So, we have made significant progress, and I think the draft 4 we are working on has captured most of this.

What is the importance of design thinking? Design thinking makes the user paramount, ensuring that services we end up will do the job they are supposed to, as well as delighting the customer.

Design thinking and methods provide new routes to better public services that meet people's needs and deliver value for money. That is the key.

We have been making tablets for 100 years or more. It is a design problem. We essentially have not used the vocabulary, we haven't brought that in. Tools, such as pre-formulation characterization, and so forth, literally have become [inaudible], but that information often is

missing in our assessment.

So, if I distinguish between conventional and novel design for the sake of distinction in terms of how we use prior knowledge, the key aspect of this design and quality relationship is utility of prior knowledge. For similar drug products, you have probably more prior knowledge, and for novel designs, you have to rely more on the experiments you generate, but prior knowledge is the key.

If you are going to come with a new tablet formulation, and you have 300 similar tablet formulations on the market, how much more information do we need? If you leverage the prior knowledge correctly and characterize your drug substance in a way to say all right, this is the way it is, you can leverage that knowledge.

Level of mechanistic understanding will depend, will vary. Pre-formulation programs, many good pre-formulation programs get to the mechanism of degradation, get to the mechanism of absorption including Bioform Classification System, characterization, that is the fundamental. That

defines literally every aspect of the manufacturing process and other things.

So, if you have that information, if you will not be mechanistic completely, but you have valuable information, that moves forward.

The challenge I think is to think about design during drug development. As you develop your characterization and your development program, you have to keep in mind the ability to reliably predict performance, confirm as you progress. Every experiment you do next, say, a scale-up, is adding to your knowledge base, is a means to evaluate the predictability of your prior knowledge, and so forth.

So, if you think about designing the entire development project from a design prospective, and capturing your predictability, you actually have an opportunity to move forward very quickly in terms of regulatory aspects, as well.

So, level of understanding increases over time, and I think we have to recognize that. Structured empirical approach is often necessary

because you often are not mechanistic.

Use of prior knowledge to identify and select a design space for characterization is fundamental, and I think Ken Morris mentioned this yesterday. People often jump into design of experiments without knowing what design space they want to explore.

If you miss the prior knowledge, you actually increase your workload, you increase your cost by not being intelligent enough to say what are the critical variables upfront, and sort of exploring the design space. You cannot approach this in a blinded fashion.

For example, now, if you have multiple number of variables that you have to study, obviously, you cannot study all of them. That is where risk comes in. Prior knowledge and risk assessment is the way to address that, for example, failure mode effect analysis would be a means to say all right, these are the critical variables, at least these are potential critical variables, these are the ones we will select and move forward.

So, initial conditions for screening experiments and then experimental conditions are then dependent on this prior knowledge and risk assessment.

Impact of formulation and process factors on performance, why can't we leverage and be more intelligent about our clinical trial material itself, and how do we design clinical trials, because that is where the connection between quality and clinical comes together, and I will show you an example as we go.

Similarly, with shelf life. If you are getting mechanistic understanding, and so forth, prior knowledge and shelf life, I think is a wonderful opportunity which we don't utilize today.

Just to give you an example, these are standard procedures in industry. Here, is a work from Amgen in a sense how do they address the large number of variables as they go through process characterization, pre-characterization experiments, is to bring the prior knowledge to bear on this.

So, process characterization studies start

with pre-characterization work, screening experiments, interactions, and combinations of key parameters leading to process redundancy.

They sort of covered that with a formal risk analysis. So, these are standard procedures, and in many, many aspects, the formulation development process has built in robust approaches, but it is not formalized, it is not well understood.

What is a robust design? A robust design is not removing the source of variability, but designing a process or product to reduce the variability.

A very simple example that in pharmaceuticals we have, is we know magnesium stearate is a wonderful lubricant, but it has a drawback of affecting dissolution, we know that.

Half of the formulations that we have in our submissions actually have a robust design built in. They will use a smaller model on sodium lauryl sulfate. That negates the negative effect of magnesium stearate. We have known that as

pharmacists, formulators, and so forth, a long period of time, but we never captured that as a knowledge base.

If you are making a tablet, you are compacting. Compaction has an effect on dissolution. If you have right amount of disintegrating agent, you remove the effect of compaction force. It's as simple as that. That is what a robust design principle brings to bear on that.

What is troubling often is, if you look at the SUPAC guidance, and if you look at the way we have regulated, the way we have done experiments often is to define our input or independent variables in terms of equipment. Say, for example, if you look at the SUPAC guidance, we say equipment of same design and operating principles, you can do this, and so forth.

That is not a quantifiable. It is an identifier. So, we know that performance of a unit operation depends on material characteristics, particle attributes, equipment design, and

operating conditions.

Instead of sort of defining of input as equipment A, equipment B, and equipment C, and then doing a design experiment, if you are smarter, you will say all right, what are the forces acting on the particle irrespective of the equipment design. That removes that and improves your ability to generalize. So these principles have been there for 60 years.

Let me explain, in a sense, I think the key aspect here is risk-based specifications. Here, is an ICH Q6A decision tree. Let me walk you through this.

What specific test conditions and acceptance criteria are appropriate for a conventional or immediate release dosage form?

Now, Professor Nozer corrected me before, so I will correct myself again. He said this is not a decision tree, this is an event tree.

Question 1 is: Dissolution significantly affects bioavailability? That is the Question 1.

If the answer is yes, develop test

conditions and acceptance criteria to distinguish between unacceptable bioavailability.

But if the answer is no, you go down. Do changes in formulation or manufacturing variables affect dissolution?

If the answer is no, go down. Adopt appropriate test conditions and acceptance criteria without regard to discriminating power, to pass clinically acceptable batches.

The first question is how do you know dissolution significantly affects viability. Most NDAs, not all, have a simple test that they do. It is called a "Related bioavailability study." They will compare a solution with a solid dosage form, and often you see they are superimposable. That means dissolution is not rate limiting. So, dissolution is not likely to affect that.

Do changes in formulation variables affect dissolution? Yes, all of them do, most of them do.

If the answer is no, for heaven's sake, if you can find a formulation that doesn't have that, but you still put a dissolution test. The question

should be why, why do you need that dissolution test?

So, some of the questions, how, why, and what really have not been addressed adequately, and our dissolution specification setting is one, two, three, these were your three batches, this is your specification. Often, it is limited to that.

I want to remind you that variability is inherent, and I did include a paper in your packet. This was published recently from Cambridge University and Pfizer.

It said if you don't account for variability and you assume that meeting specification means you are bioequivalent, that may not always be true. In fact, if you do this analysis, if your specifications are not set right, you have a 50-50 chance whether you are bioequivalent or not, or whether you meet specification or not.

So specifications for dissolution are not likely to be the ones ensuring bioequivalence. It is the entire control process that does that, but

we focus so much attention on just one test, we miss the whole point.

Let me come back to this decision tree. I think in a quality by design thinking, this is what are my questions. So, dissolution significantly affect bioavailability is a product design issue. You start with your pre-formulation, your biopharm classification, the solubility, permeability, and all that aspect, and you have an anticipation whether it will be affected or not, so when you do your related bioavailability study, you are conforming your past prior knowledge.

So, postulate-confirmed based on mechanism or empirically, and that can apply to the question dissolution significantly affect bioavailability or do changes in formulation affect dissolution or not.

But Jurgen points out, the key question is we have a mind-set 80 to 125, and that is the magic number. Where did that magic number come from? I think this is where the clinical relevance comes in, what is a relevant acceptance criteria to judge

whether an acceptable bioavailability is there or not, and that is a clinical pharmacology question. That is where we link to the clinic.

If you have a good PK/PD assessment, and so forth, you have far more information available to make a more rational judgment, and that is the question there.

So, design of manufacturing and controls, and the question is how reliable those are, do changes in formulation and manufacturing variables affect dissolution? If the answer is yes, Are these changes controlled by another procedure and acceptance criteria?

If the answer is yes, we come back and put a dissolution test. My question is why? If the dissolution test itself is variable, and so forth, why would you want to put another test? You have a series of tests, and so forth, your chances of failure keeps increasing.

So, the questions that we need to ask are: How good or how reliable are your design and controls that you have put in place for particle

size, morphic form, and so forth, to address these conditions?

So, overall risk-based CMC would ask why for these questions, but also, so what? If dissolution is not rate-limiting, the question should be so what, why do we need a dissolution test, and so forth.

So, this is how it all sort of comes out. So, quality by design thinking brings an overall CMC systems approach, for example, link to morphic form, particle size, stability failure mechanisms, and so forth, to address this in a systematic way.

Continuous improvement is not possible today, because any movement is a change. This is a direct cut-and-paste from our SUPAC guidance. Level 1 change, definition of change is this category includes process changes including changes such as mixing times and operating speeds within application/validation ranges.

If you need to have validated those ranges, any movement within that is a change today. So, it requires to be reported. If you change

outside those ranges, you not only have to report it, but then you have to do a Case B dissolution, which is a profile comparison, and the supplement, and the stability, and so forth, so today, it is not possible.

Our law and our regulations provide provisions for those approaches, and this is a Section 506A of the Act and 314.70 that we issued. We are required to make decisions based on potential to have an adverse effect on identity, strength, quality, purity, or potency of the drug product.

We have used the phrases "substantial," "moderate," and "minimal." They are not very useful, they are not probabilistic, and I think that is where we have to work at.

But also, if you look at CFR 314.70, there is a provision no change means no reporting beyond the variations already provided in the application, and that is where the design space comes in.

So, what is this design space? The design space is simply a space of knowledge or information

where you know you will not affect your bioavailability, you will not affect your stability, and you will be in specification, but you are improving the manufacturing efficiency, you are improving the manufacturing process through new equipment, better controls through process adjustment in response to incoming input variables, and so forth.

So, that is what continuous improvement is, and Box defined this years ago as evolutionary operations.

So, that is how ICH Q8 information that brings reliability to your deliver design information, ICH Q9, which will develop the failure mode effect analysis and risk communication, too, all of them come together to define a design space for continuous improvement, and that design space will depend on the company's information that sort of comes about.

You will know which area is the change, which area is not a change, and that is the map of Maryland, a weather map, so you shouldn't be in the

red area. That's about it.

Yesterday, Steve showed this slide that I had developed for thinking about the entire system, how do you connect the dots. I am not going to get into that, but I think the key aspect there is the knowledge space, and the knowledge space in relation to the clinical knowledge space and in relation to the manufacturing knowledge space all have to come together to sort of address this.

A personal learning that I had going through the GMP process is a better appreciation for quality system. I am still an academic at heart, and when you put me into a documentation mode, I get nervous, and great mounds of paper is something I want to avoid.

The quality system that we have worked out in the GMP Initiative is actually quite nice and simple. It says say what you do, do what you say, prove it, and improve it. Those are the fundamental principles.

So, say what you do to FDA, is your pharmaceutical development information that you

share with us? If you say this is all I know, so that is what you are going to get. If you say this is how much I know, and so forth, you get benefits from that, but then you have to do what you say consistently. You have to prove it, and if you are unable to prove it, you have to ask why, and you have corrective actions.

If you are unable to ask why, unable to answer why, then, there is a risk profile that increases. And prove it is more optional, there is continuous improvement in innovation sort of comes in there.

The challenges, I think in pharmacy, in pharmaceutical education, we have been doing this all along. What has been missing is a formal structure and communication tool.

I draw some similarity here. If I look at what has happened in chemical engineering, and now I think chemical engineering is going through soul-searching activities to redefine themselves, but this is how chemical engineering evolved.

It started with industrial chemistry, unit

operations, material and energy balance, chemical engineering thermodynamics and control, applied kinetics, process design, transport phenomena, process dynamics, process engineering. Now, they are in molecular transformation, multi-scale analysis, and systems view.

So, they went from industrial chemistry to unit operations, to chemical engineering science, to system engineering.

Industrial pharmacy is still industrial pharmacy in the U.S., not as well in Japan, China, Europe, it's a pharmaceutical engineering degree literally. So, we are still in that, and I think we can catch up on that, going to bring some of those principles.

It is important to do that, it is important to bring a systems engineering perspective because not only we have to deal with the traditional goals of quality, the GMP Initiative offered new, non-traditional goals, that is, risk-based, flexibility, robustness, scalability, continuous improvement, innovation,

and efficiency. These are typically non-traditional goals.

The characteristics of these goals are complexity and uncertainty associated with that. The relationship between goals and characteristics that we are seeking is knowledge and information centric relationships.

There are fundamental issues there, because if you don't get to this, our quality system will continue to be a paper chase exercise, and not really get to the heart of it, because we don't want to be lurching from fact to fact, from one quality system to another. Unless this process is in the same sciences there, this will not happen.

I will skip that and focus on where we are. My assessment is this. This is not rocket science, this is straightforward and simple for those who have been in this area for quite some time. For those who are not, there is a need for education training.

There are signs that I see. The phone

call this morning from a major company, and, in fact, I should have asked that I can share the name or not. Their positive experience with the development report already in a four-cycle review is a good example that our folks can manage this process well, but consistency and making sure it happens consistently is a challenge.

So, the immediate education need that I see going through the PAT training, and so forth. Now, for a broader training is introduction to statistical quality control. That is fundamental. We are missing that, and I emphasize it is not biostatistics. There is a distinction between statistical quality control and biostatistics, hypothesis testing, and where we keep missing that.

I meet with the PhRMA Statistics Group, and so forth. It comes back we are missing the quality dimension here. We have to understand variability. We have to focus and put training programs on molecular pharmaceutics and biopharmaceutics.

We have gone to the molecular level in

most of those areas. Engineering principles is a key aspect. Risk assessment and communication would be a program. All of this will come together quite nicely with the ICH Q8/Q9 training program itself, but I think we would like to add some additional training.

I know Ken has been working with us quite constantly on focusing on what the right questions are for the review process, but I think we can put a more formal training program on all of these aspects.

I would like to say systems approach and thinking is important. Unfortunately, most of the training programs that we go through, our BS/MS/BA programs actually takes us away from systems thinking to focus as narrowly as possible, and so forth, but in an applied area in the regulatory setting like this, systems thinking is important.

Unfortunately, I go and talk about Deming, many people in the industry have never heard of the name Deming. I think we need to introduce people to Deming and others.

Team building and communication will be the key.

I will end my talk saying that coming together is a beginning, keeping together is progress, working together is success.

The GMP Initiative brought us together. I think the PAT Initiative took us further, and a smaller group is actually making progress.

I am fairly positive. I went through a quite depressive cycle in some of the challenges, and so forth, but I am fairly positive that I think we are on the right track, and we will achieve this rather quickly.

Policy Gap Analysis

MR. CLARK: I am going to deliver a talk about something of the policy gap, but what I will really be talking about is a guidance development process and some changes that we have done there. My talk will be quite pedestrian and quite short, which I hope to be some relief.

I noticed in the agenda, at 10:30 we were supposed to break, but now it's after 11:00, and

were this agenda an application, we would be found in violation of an agreement, and if we showed a pattern of being late, well, we might just be under a consent decree. So, I think we are at some risk, so I will move us along and try to get us back on the path of righteousness, and such.

I want to point out that somebody mentioned earlier today about failure, about failure data, I am sorry I didn't quite catalog who it was that brought it up, but the failure of data to point stayed in my mind.

One of the things that we will be talking about in Yokohama in Q8 is what role that plays in an application, and to help define a design space, is there a place for us to use that in an evaluation of an application, and if you have determined where your system fails, can that offer you some relief as to where you operate. I wanted to just bring that point up as I start in this speech.

In the GMPs for the 21st Century, some CMC guidance documents are out of synchronization with

that rollout that you all have seen by now, but the guidance process that developed these documents has strong and weak points, and one of the main strengths of this is the technical input from our staff, from our review staff.

One of our weaknesses is in the decisionmaking process for actually moving the documents from step to step and getting them out, which causes it to be very slow.

I would like to really dwell on the strength. One of the things that we need to take away from our previous guidance development process is that these deliberative processes are well meaning, and these people are highly trained, and they are experts at what they do. At every step, they are trying to articulate the things that are on their minds and how to get applications approved in the best way.

They may have become proscriptive and prescriptive, but that is not a failure in their attempts to articulate the best way to get an application approved.

We believe that there may be a better way to articulate that point, and obviously, with the rollout, and you compare the rollout to the documents that we have on our guidance page, there is the gap, and most people know that, that are familiar with the two sets of documents, so I will move on from there.

The draft cycling that was the weak point, I will point out this is the old draft cycling, and you will see that there was a CMCCC working group assigned from a CMCCC committee body. That CMCCC would define a group to work, and we will call that the body for now, to develop a document.

They would go ahead and develop a document, and this might take six months, and it might take two years, and it might take five years, but they would develop an articulation of the areas of interest for that document.

They would then proceed to take that and go through each review team, through some kind of a hierarchical structure in the organization. Those review teams would then have comments, not unlike

the public comment system, and those comments would go back to that review group, and they would redraft the document, which might take another year or two.

Because these people are not dedicated to that task, they are also reviewing drugs, they are also involved in a lot of other efforts like ACPS, and they are also involved in guidance development.

So, they go back to the review teams, goes back to that CMCCC body, and then it goes back up to the working group or back up to the committee for review, and then from the committee, it goes to an OPS editor.

Now, that process, those steps might take as much as six months, it might be a year. The OPS editors then have a go at making sure that the legal language is current with the desires of our legal staff, and they might pass it on to the legal edit if their suggestions are minimal, and so on.

If not, if the suggestions are strong and get into the body of the document to a large degree, it might actually go right back up to the

body and have to go all through all that stuff I just mentioned all over again, and were I mean-spirited, I could go through it a second time, but I won't.

Well, you go to the legal edit, then, it goes out to public comment. Then, you have public comments dockets come back. You might have 1,000 comments if you are lucky. It might be a couple inches thick if you are lucky, and it might be a foot high if you are not so lucky.

If that happens, well, it will happen, then, you have to catalog all those comments, address each of them somehow, address them by groups or individually, and then if you have to make substantial changes to the document in order to address those comments, go back up to the top, and if I were extra mean-spirited, we could go through this whole thing again.

I think you can understand that that could be a laborious process, and that is my excuse for why guidances take so long to get out of the Agency.

When somebody says that a guidance will be available soon, they may think it is going to be available soon, because they think they are near the end of the process, or what they don't maybe not understand is that there is an iteration that they hadn't predicted. So, that is something we have been dealing with over the years.

This is a slide that puts into words some of what we just discussed, but it also points out that there is a rapid change in FDA thinking over the last couple of years. It leaves slower efforts to catch up. The guidance development is, in fact, a slower process.

There is an investment of time, and the documents may be slow, but they have a lot of momentum. You have that many people working that hard, that many smart people working that hard over that many years, and the document gets momentum.

The guidance content and the new direction are managed actually by two different groups. We have this OPS policy direction setting group, which had some involvement from the reviewers and staff,

but the guidance content was being managed by the review staff directly with reciprocal input from the higher end, the OPS level.

We have taken some actions to try to remedy the situation. We have moved coordinating and decisionmaking from the CMCCC working group to an OPS office level group, and have created the OPS CC. Helen mentioned that a little earlier. They have a lot of tasks, one of which will be to help us coordinate these guidance documents.

It will move guidance content management up to OPS with some lookback down to the review level when we need that expertise that is at the review level.

We disbanded the CMCCC as such, as words. Of course, we have the same people wearing hats with new letters on them, OPS CC, but it has a different function, and I will show you that in the next slide.

The mandate through OPS CC is to recruit technical input from scientists when we need it.

The new process looks something like what

I have on the board now, where you have OPS CC actually managing the creation of the documents, getting science input from selected teams, getting input back to OPS CC. Then, you have a smoother process on the high end of that document formation process. So, we hope that that will shorten things up a bit up there. It might take 10 or so years off the process, which should improve things.

The OPS edit and the legal edit have never really been hugely time-consuming except that they can cause reiterations, but it is that iteration that we have tried to smooth out. Of course, the public comment isn't changing. We still have the dockets and dockets management.

We are trying to synchronize the effort, but there are a number of techniques we intend to use to synchronize the effort of guidances with the rollout of the two-year effort in the GMPs for the 21st Century.

One is, of course, obviously, a revision of drafts. We have drafts out there. We have public comments that are available for many of

those drafts, bring those in, and we might actually put out for a second draft some of these documents, because we may incorporate public comment, we may incorporate some of the new thinking, and if the document is substantially changed, we may not go from draft to final. We may go from draft to public draft to get more comment.

Another option is the withdrawal of documents. I would see that option mainly for finalized guidance documents that just have become obsolete, and perhaps no longer do any good for us, so we may actually consider withdrawing some of them. We have done this in the past, and we may seek to do it in the future.

Another effort is enforcement discretion. We may actually use guidance to bring into line more of our practice where sometimes a practice has found its way into regulation, where the regulation will require you to do something that we really don't necessarily believe is constructive at this point anymore, and we may use guidance to iterate an enforcement discretion over some terms to

address some of the regulation requirements. That would pretty much be viewed as a precursor to actually revising the regulation itself.

There is also a consideration of options in OTG other than guidance. The question and answer format where we have a simple question and we want to answer it with a paragraph and hopefully, it doesn't turn into a chapter, we post it on public Internet, try to keep it simple.

It would go through our guidance procedure, but hopefully, be much quicker, and not try to address a large range of things, but just to keep it to one topic, keep it simple.

We also want to look into a Manual of Policy Procedures, to expand that. I don't believe that we have actually exploited our Manuals of Policy and Procedures enough to articulate what we would like our internal staff to be doing, have it in an if/then format, directed toward OPS staff.

What is nice about the Manuals of Policies and Procedures is that they are publicly available once we are done, and they are rapid. They can be

rapid to get out, and we have more flexibility in what we say in them.

Back to guidances in particular. We really would like to have a more risk-based approach expressed in the guidance, reverse recent tendency toward proscription and prescription, which I think that if anyone has read some of the recent drafts, you can see there is a difference between what was published in 1987 and what we have been publishing in recent times, and that they tend to be much more detailed and much more instructive as to exactly what you should be doing.

We try to get up to a higher level and try to rely more on the science for the specific issues to drive the decisions that are made.

The manufacturer should choose the technology and the approach to problem solving where we should be evaluating more of the science behind whether or not the quality, the ongoing quality is short, and as Ajaz put up there earlier, what is the acceptably low probability of not meeting the clinical intent.

Focus efforts on assurance of reliable product quality, and not on technology.

Input into our processes is one of the things I would like to propose here, is for this body to seriously consider, creating a fact-finding group to help us with guidance processes.

Is there a potential gain from formation of this fact-finding group to help us determine how we move forward to the desired state?

Some of the questions that fact-finding group would be asking or asking and answering would be: Do we need all the guidances that we have now? Where are they incongruent? Provide advice as to what guidance industry needs as we work toward a new regulatory paradigm, and what should be the prioritization of those documents if we have any of them at all.

So, I would like to propose that this body be engaged in that effort at some level to be deciding who would be on that body and, of course, it would be within the rules of the advisory committee system.

That is the end of my talk. Since I am the last of the three, I guess I will stay at the podium and be the target for the questions.

DR. KIBBE: It depends on how much time the other two speakers will need and how much time we allow for questions. We can always come back to the topic after the lunch break, but if there are some quick questions, we can handle, Nozer?

DR. SINGPURWALLA: Not quick. I have lots of questions for Ajaz, and I am sure he expects those. So, perhaps we should postpone them until another avenue, or I can privately communicate.

DR. KIBBE: No, we will get to them. I want them on the record.

Go ahead.

DR. MEYER: Just one quick comment. I like the idea of a question and answer format in a public Internet, frequently asked question kind of thing. I think that would save the Agency some time. It will be easy for the sponsors. You won't have to deal with repeat questions, so I think that would be a step forward to have that.

MR. CLARK: Thank you, Committee, thank you, Dr. Kibbe.

DR. KIBBE: Meryl, go ahead.

DR. KAROL: I have heard throughout this morning about the risk-based approach towards your changes, and I wondered what do you have in mind for training and education of the personnel in order to make them knowledgeable about risk-based approaches?

MR. CLARK: The training of the personnel is really an ongoing thing. It isn't really a here it starts and here it ends. We have the people involved. We have a peer review system that Moheb has set up where they come together after they have finished a review, and they present it to their colleagues.

We, from the Policy Groups, we go in and we listen. We have comments. We steer them, we try to steer them toward the things that have been done well, and to bring that out. A lot of the practices that are involved in a review of an application are, in fact, risk-based practices, and

sometimes a reviewer just doesn't bring that up to the surface and make that well known.

Part of our role in that particular venue is to point that out, to say, well, you took a risk-based decision here, we would just like you to bring that up to the surface and make it the theme of the document as opposed to going down into the technology and making that the backbone.

So, it isn't really a big stretch for these people to grasp onto it. They are all very highly trained.

We do have training programs in mind. We haven't really implemented a lot of them upfront yet, but the goal is to have a top-down approach. Dr. Morris has been involved at some level at helping us train managers into the thinking and to work that down through the management levels.

We have gotten down to the team leader level at their last presentation, but the rollout did take up all our resources up until just now. So, we will be re-initiating that effort.

DR. KIBBE: Jurgen.

DR. VENITZ: A few comments, one more fundamental comment to Jon's presentation that has to do with my favorite word, and that is risk. You talk about how risk is being assessed, and you have emphasized primarily the probabilistic component, that you have tried to predict the likelihood of something happens.

Well, risk has a second component, and that is a judgment, how bad is what you measure, or how potentially bad can it be. I think one of the things that you will face is within the Agency, is this culture of always assuming the worst, anything that happens we can assess whether that happens often or not is bad.

Well, risk really requires you to make a judgment as to how bad or how not as bad it might be. So, I am just pointing that out, risk is not just measuring probabilities, but it is also assigning utility values to those probabilities.

Two small comments to Helen's presentation. I would encourage, especially with all the changes that are occurring, that your staff

participate in all those industry meetings, particularly the pre-IND and the end of Phase II meetings, because I am pretty sure that is where a lot of things are being discussed that are relevant to the change in GMP and PAT, and what have you.

As far as the briefings are concerned, you might consider something like a question-based review where not the entire material gets reviewed, but you are actually focusing in on things like source variability on things that are potentially at risk.

DR. KIBBE: Thank you, Jurgen. What we really were hoping for is if you had a quick question, because I want to get the next two things out. If you have got a long discussion, we will do it right after lunch.

Let's go ahead and get Mr. Ahmed to talk about the FDA Critical Path Initiative, a generic industry perspective.

Generic Pharmaceutical Association Perspective

MR. AHMED: Good morning, everybody.

Sorry for this delayed presentation. I

know a lot of you must be looking for a break, but just bear with me. It's not that bad. It will be fairly short because I am presenting from a generic perspective, and clearly, the Critical Path Initiative does not really look into the generic industry the way other presentations or the Internet on the FDA web site.

First of all, I would like to thank Helen and everybody at the Agency for providing GPhA the opportunity to present their view regarding the Critical Path Initiative.

Gordon actually asked me to do this presentation on behalf of GPhA. I am from American Pharmaceutical Partners, which is a direct injectable manufacturer. We have a proprietary drug under review right now at the FDA.

What I am going to talk about, first, is what is the overview of generic industry, what part the generic industry really plays in the health care system in the United States, the Critical Path Initiative concept, the benefits of the Critical Path Initiative to both the generic industry, as

well as the innovator companies.

I think one of the most important component of the U.S. health care system is generic industry, as you can see. Fifty-one percent of the prescriptions dispensed in the United States were generic drugs. This data is based on the 2003 IMS data. I am sure the utilization of drugs will increase as time goes by.

About 8 percent of overall cost of prescription drugs is contributed by the generics. There are several off-patent products which still don't have any generic competition, and that is really hurting the consumer in a lot of respects, because these products have been off patent for a while, and I will elaborate on those as I go on.

When we reviewed the Critical Path Initiative, we found that it really provides significantly improved tools for evaluating basically safety, efficacy, and characterization of the drug substance like the product/manufacturing, because I think this is a very bold concept proposed by the Agency, because over the last

15-plus years I have been dealing with the Agency, this is really a breath of fresh air, because I still hear that titration is a better method than is HPLC, because it's in the USP, so this is really very good thinking on the part of the Agency.

We have got to get out of that mode, because, on the one hand, we hear from FDA good science, good science, good science. We file an application and provide a better method to the Agency. There is now we like potential metric titration because in the USP, your HPLC method or LCMS method is not good.

So, I think this is a good shift. At least from our standpoint, we think that science really holds a lot more promise and can hoe a lot more ground than regulations.

We like FDA's approach. We like the collaborative approach. I think it is important that we involve the academics, the patient groups, the industry, as well as the regulatory bodies, because really at the end of the day, all of us have the same function, which is to protect the

American public and to provide a service, because the drugs used by folks is really for people who are unfortunate, because they have to use those drugs, so we have to make sure that we provide the highest quality product, which is the most efficacious and has the lowest side effect.

The desired outcome meaning yes, faster approvals. Again, a little bit of a misnomer because just to give an example, we filed for a CB30 to extend expiration dating for a very critical product.

It took FDA 60 days to first acknowledge that we filed the CB30, and then it will be another six months before we make a decision, so what is the point in filing a CB30? That is what I really wanted to bring to Helen. If we want the desired outcome to be faster, let's please be more pragmatic, because if it is built around the system the way it is right now, the desired objective is really very far away.

Again, the primary emphasis is on discovery, and it really helps pharma, and clearly,

we are a big proponent of that because what pharma produces eventually has the opportunity to become a generic, so we are imploring the Agency to work with pharma to enhance drug development process and give the pharma folks faster approvals.

From a generic industry perspective, I think the Critical Path Initiative is also very helpful, and I request Helen and Ajaz and everybody else to really think it hard because the generic industry represents a big opportunity for the American health care system, as well as for the Agency itself.

We would like to be part of this initiative because there are lot of opportunities where we can minimize the pains we go through on a daily basis, as well as you folks.

Again, the goal here is to have timely submissions as well as timely approvals, so the consumer can benefit. As you know, the prices, when the product becomes generic, almost within the three months, the price of the generic drug is almost 90 percent less than the innovator product,

so very clearly it helps the American public significantly from a financial standpoint.

Again, we very earnestly request the Agency to really look into providing guidance to MDIs. As all of you know, it took seven years for Albuterol to become generic. We don't want to go through that scenario again. There are still a lot of products which there is no guidance for.

The products, especially the transdermal products, which have no guidance, the inhalation products, there is still no guidance, and also, again, I don't want to take anything away from Ajaz's PAT Initiative, but in the entire PAT Initiative, there is no mention of sterile products, and currently, in the United States, about 20 percent of prescription drugs are sterile products, which includes parenterals, which includes inhalation products and topical products.

So, I would really again urge FDA to look into how they can help the sterile product manufacturers in terms of providing guidance and reducing regulatory burden. Clearly, we are

looking for better collaboration with FDA. We would like to be partners with FDA in every respect we can, but again it's a two-way street.

Sometimes we get a lot of resistance from OGD in terms of pestering them too much or in terms of arguing on scientific issues, so we really would like to have a more collaborative effort.

As part of GPhA, I would really urge FDA to look into it in terms of what our objective is, to make the safest product, but apparently there are some scientific disagreements at times, and we want to minimize the pains we go through in terms of the review process.

Lastly, I would like to talk about the 21st Century Pharmaceutical GMP Initiative. I think it's a step in the right direction, but there are a lot of issues we really need to look very hard at. One of the issues is inspection.

There is so much inconsistency in the inspection process, and to give you an example, an inspector going to a sterile manufacturing facility in New Mexico really does not even cover one-tenth

of what is covered in the Chicago District.

So, like we are from the Chicago District and we get the highest scrutiny, I can tell you that for a fact. Susan Bradley basically really keeps us on our toes, but there is so much inconsistency as I go from district to district. Please look into this because this really hurts the generic manufacturers especially because of the patent issue, and things like that.

The other think is I keep on hearing the Science-based Initiative, Science-based Initiative, but we are still getting questions from the reviewing chemists, which is really a total waste of time for us and you both, the reason being that we cannot change basic science, and nobody can change basic science.

But to give you an example, not too long ago I got a request from a reviewing chemist asking me to provide a chromatogram for mannitol where the quantitation was 229 nanometers, and I picked up the phone and called the reviewing chemist and I said, "Please, mannitol has no pi bonds, they are

all sigma bonds," and I [inaudible] off any sigma bond which the electrons could be transferred to sigma star at 220 nanometers."

He said, "I still want to look at the chromatogram." So, please, please be open-minded, please listen to the folks who really do this for a living. They know the science. They would not present data which does not make sense.

So, that is part of the 21st Century Pharmaceutical GMP Initiative. Let's be open-minded, let's discuss with the industry, because we folks, we put a lot of time and effort in terms of manufacturing batches, testing batches, and we want to produce the highest quality product and to have the minimum risk.

However, we need to be very open-minded. We need to depend on science rather than regulation.

Thank you.

DR. KIBBE: Judy has a question.

DR. BOEHLERT: I have a comment. I am going to help you out. You said you had a problem

with USP methods, titrations. Well, I have several solutions for you.

First of all, USP would love to get your HPLC method. Second of all, USP allows the use of alternate methods, so as long as your HPLC method is equivalent to a better titration, you may use it.

Now you have got the FDA to deal with. They are talking about risk, and they are talking about science. I would hope that the FDA would look at a submission favorably if you have demonstrated that your HPLC method is equivalent to the titration method and the compendium, and you can go forward.

I know you probably do get questions along those lines, but I think we need to move past that and ask the right questions.

MR. AHMED: Judy, what happens is that they say yes, HPLC method is better assurance than equivalence data, so what is the point? If you are showing equivalence data, then, what is the point of using HPLC method?

DR. BOEHLERT: Well, because you don't have to do the titration, and you really do get better data with the HPLC method.

MR. AHMED: That is what my point is.

DR. BOEHLERT: Titration might be a great method for releasing product, that you might want to use HPLC particularly during development to learn more about your product.

MR. AHMED: And like we are providing a stability indicating method, and we are telling the reviewing chemist, please, titration cannot predict the stability indicating nature of the product, and still we are asked to provide comparative data. So, that is what my point is.

DR. BOEHLERT: I know that that happens, and it happens to the pioneer industry, as well as the generic industry. We need to get past those questions that really aren't meaningful and deal with really the scientific issues and look at what the risk is of some of these decisions that are made.

MR. AHMED: Exactly.

DR. BOEHLERT: So, no, I support what you are saying.

MR. AHMED: Thank you, because we know FDA has very limited resources. We don't want to waste your time in terms of providing meaningless data.

DR. KIBBE: Thank you.

MR. AHMED: Any other questions? Thank you.

DR. KIBBE: Gerry, you have the last word.

Pharmaceutical Research and Manufacturers of America (PhRMA) Perspective

DR. MIGLIACCIO: Three weeks ago, the FDA released their final report on the 21st Century Initiative. This morning, Helen, Jon, and Ajaz talked about some gaps to achieving what was defined in that final report.

That final report did a very good job of defining the desired state, and I am not sure how many of the committee members have gone through the entire report. I had 12 hours on a flight to Tokyo, and I couldn't get through it all, but it does a very comprehensive job of painting the

desired state. Yes, there are gaps in the FDA and yes, there are gaps in industry.

In the time that I have, I am not going to give PhRMA perspectives on every element of the final report. What I will do is touch on certain elements of it.

I want to reinforce what Helen said earlier about culture change, make a couple of general comments on the report, and then talk about three of the documents in the final report, the Quality Systems guidance, the risk-based inspection model, and the ONDC risk-based quality assessment system, and then finally, summarize before lunch.

Three years of culture change. It's a two-year process, but we have been working on this for a lot longer than two years. In fact, I contend that we have been working on this for three to four years, and the culture is changing.

It is changing, it's gradual, in some cases it is dramatic and others, but there has been in this unprecedented period of communication and learning for both the industry and for FDA, and

that has really been driven by the, first of all, having a shared vision of what the desired state is, maybe not always agreeing on how to get to the desired state, but at least having the shared vision of where we wanted to get to, and having open communications about that.

PAT was the model, and much has followed based on the model.

We, in industry, are moving from a fear of data to a passion for process understanding. Now, let me describe that fear of data. I grew up in this industry, I have been in it for 25 years, and I remember the days in the laboratory where I did some testing that was not required by the documents in my NDA, and getting reprimanded for doing any testing that was not required and where I did not have a clear understanding of how I was going to deal with the data.

Well, we are getting much better now, we are using much more sophisticated tools at converting data into knowledge, and therefore, the fear of just data generation is going away, and we

are also learning very rapidly that that data, if converted properly into process understanding, process knowledge, can tell us a lot about our processes, can tell us where the variability is, and can help us remove that variability where it is excessive.

The next point, science, not blind compliance, is winning the day more often. I am seeing this both internally and I am seeing it during inspections by FDA, that there is much more discussion. There is much more discussion about the science, and I certainly, from my perspective in the industry, and I see my colleagues, as well, in other companies, they are using the science to make decisions much more frequently than simply sitting back and saying I am not going to take a risk, blind compliance, this is what the Agency expects, and just ignore the science. So, that is going away.

I think you are finding in many companies, innovation is accelerating, and a lot of it has to do with the open dialogue and the encouragement of

the Agency obviously in this area.

Interactions during inspections are changing, and I think some companies have seen dramatic changes, others subtle changes, but Helen talked I guess yesterday about the dispute resolution process, and I think that the discussions leading up to the guidance, the draft guidance, have had a significant impact on the way both our firms and the FDA investigators approach an investigation or an inspection.

We are far more willing to put much more scientific knowledge on the table during an inspection. Why? Because basically, the dispute resolution process says that if you are going to dispute a scientific issue, you have to use what you have presented during the inspection, so we want to make sure we get that information out.

Most of used to sit there and say, all right, we will wait to see if the investigator puts it on the 483, and if they put it on the 483, then, we will provide a written response to dispute it.

Well, now, we are dealing with it during

the inspection, and now the investigators are taking the time to look at the science, and they are calling in outside help when they need it to review the science, and we are seeing more and more issues resolved during the inspection, or shortly after the inspection with the district.

So, I think the dialogue about dispute resolution has taken us 90 percent of the way to dealing with scientific disputes.

So, some general comments on the final report. I think this is a Churchill quote. "This is not the end, it is the beginning." The infrastructure is in place, but we have a lot to do.

We applaud the magnitude of what has been accomplished, and not so much the volume of work that was accomplished by FDA with assistance from industry and academia, but the rigor.

If you look at these documents carefully, it is not individuals sitting around and putting their own thoughts on paper, but bringing in experts from various fields, including risk

management, and ensuring that the documents had the technical content that was required to achieve the objective.

We obviously, in both industry and FDA, need to continue to work together to make sure that what is in those documents is fully understood throughout the Agency and throughout industry, and modified as appropriate, and then implemented. So, we have a lot more to accomplish.

Let me now turn to three of the documents that were in there.

First of all, the Quality Systems guidance, and this is the Quality Systems guidance for industry. We were very pleased to see the Quality Systems document for use within FDA. We think that is going to contribute to their operation significantly, but the guidance for industry is very comprehensive, and we think it is of great utility.

I know many companies are already using it to benchmark themselves, to look at our own Quality Systems and say how do we match up against this

document.

Now, there are some key issues in the document, and PhRMA will be commenting on this document and many others. I am just trying to point out some high-level issues, but certainly process understanding, what level of process understanding leads to flexible continuous improvement in the regulatory environment? It's a key issue and I think both Helen and Ajaz pointed that out this morning.

We believe that it is imperative that these concepts be addressed on the global level. Somebody pointed out earlier today, most of us are in global businesses, the FDA guidance on Quality Systems, we believe really lays that starting point for ICH discussions on the proposed Q10. So, we really believe that this needs to go on a global basis and can contribute globally.

There are some parts of the guidance that we need to ensure we look at, potentially revise. We need to move away from some of the current compliance systems, and get us into a Quality

Systems mode. So, I will just give you one example.

The guidance calls for the trending of data, encourages the trending of data as being part of a good Quality System structure. The problem is some of the data we generate for compliance purposes provides no value on a trending exercise.

How do you trend "none detected" or below level of quantitation? How do you trend data that is rounded down to a point where it no longer has any meaningful benefit to gaining process understanding? And why trend data that is generated that has no relationship to critical quality attributes or critical process parameters?

Our current specification system drives the collection of that data. So, we talked about specifications earlier. I think this workshop in March is going to help us move these discussions forward, but our current specification system has to evolve. It has to evolve so that we are collecting meaningful data on things that are critical to quality.

Now, let me move to the risk-based inspection model, certainly a solid step forward to allow FDA to focus on higher risk sites. We do question some of the elements of the algorithm, and we think they require further discussion.

Again, as I raised at the Manufacturing Subcommittee meeting, and Judy talked about yesterday, the concept of volume is problematic to us, because if you have a manufacturing facility that makes two or three products at very high volume, actually, they understand those processes much more than a facility that may make 20 products at lower volumes, and they are probably much better controlled. Therefore, the risk associated with high volume is probably, in many cases, much lower.

So, the use of a strict volume metric in the algorithm is problematic, and we would like to discuss that.

But our most serious concern is about the transparency of the system. These are words from the risk-based inspection model document, and what they say is that the FDA brought in experts, and

the experts have established risk weightings for various processes, products, unit operations I assume, we don't have that information, and that has all been used to determine the risk factors or the risk level of various sites, but they don't intend to publish or disclose that information.

Now, when we started this three years ago, we said one of the key objectives was that we understood where the risk was in this business, and that both industry and FDA focused on the high risk.

Another document that was issued in the final report is this defining the customer in a regulatory agency, and we are, the industry is, a customer in certain case of the Agency, especially when it comes to their guidance documents and position papers.

If you look in the middle, when FDA develops guidance documents representing the Agency's current thinking on a particular subject, we provide clarity and understanding to firms.

Well, there is no clarity and

understanding on what the FDA considers high risk in manufacturing coming out of this document. Also, in the final report, the FDA will now be using a Quality Systems approach to improve the predictability and consistency. Again, there is no predictability here.

We believe that industry and FDA have to have a mutual understanding of what processes, what unit operations are considered higher risk. We believe experts in industry should have the opportunity to discuss and potentially debate what is considered higher risk by FDA, so that both industry and FDA can focus their resources on what we mutually agree are higher risk.

We think transparency is essential here, and I truly believe this is a win-win-win, a win for FDA, a win for industry, and a win for the patients if we all agree and focus on what is high risk, but if it's not going to be published, if we are not going to understand whether the FDA perceives certain facilities as high risk, we are going to do our own risk assessment, and it may be

different. It may be different, and I don't think that is going to be an effective use of anyone's resources.

So, we feel very strongly that transparency here is essential, and we hope FDA will continue the dialogue with us on this specific model.

Finally, the ONDC risk-based assessment, quality assessment system, it represents a very profound change in the organization and review process. You heard a lot about that both yesterday and today. We support the objective strongly, but a lot of work is required to achieve the end state.

Now, on the PAT Initiative and then on the GMP or the Drug Quality Initiative, the FDA demonstrated a willingness to put the leadership in place and the resources in place to make it happen, and I think this two-year report is an evidence of that.

The question we have, a question that will we have the same commitment of leadership and of, in this case, review availability, to deal with

this initiative, and as importantly, will industry have the same input into this process as we had into the PAT and the general Drug Quality Initiative over the past two to three years. So, it is a key issue for us.

There is this potential that this proposal creates this expectation. I think, Judy, you said something about this yesterday in your summary of the Subcommittee meeting, that there is going to be a significant increase in the knowledge provided upfront.

We will be providing different information and more knowledge, yes, not necessarily more information, it is going to be more knowledge.

But again, there will be a greater degree of process understanding, but it still will be limited with the original NDA submission. It will be sufficient to establish that we have a robust process, but process understanding is a continuum and will accelerate post-approval.

So, you know, you are going to get the design space in the NDA, but that design space may

be limited. It will expand tremendously in the first one to two years of commercial manufacturing.

We believe FDA should work through ICH to establish a global partnership for the risk-based quality assessment system. Right now the assessment systems in Japan, the EU, and the U.S. are very different, and we certainly should not exacerbate the differences by moving forward with this initiative without including our global partners.

One area which we understand the motivation to go to the pre- and post-marketing approach in the quality assessment system, but it does require some further evaluation.

As I said just a few minutes ago, process understanding significantly increases during the first one to two years of marketing, and potential for continuous improvement is really the highest during that period of time, and there is certainly a value in having the reviewer who reviewed the original NDA involved in those initial continuous improvement changes.

As I said, you have got a limited design space in the NDA, and that design space is going to grow exponentially in the first couple of years.

Having to shift gears from one reviewer to another may be somewhat counterproductive. So, we think this requires further discussion as to is there an appropriate time frame where the handoff goes to postmarketing.

Helen talked this morning about two systems, potentially two review systems, one where you have the science process understanding in the application, one without. The problem is that process understanding is not a yes or no answer, it's a continuum.

So, every application, Company A may believe in this concept of manufacturing process and process understanding, but Company A's NDA for product X and for product Y will have different levels of process understanding.

How will a reviewer determine where the application is in that continuum and how it should be addressed? Key questions we think need to be

addressed between FDA and industry as we move this quality assessment system forward.

So, to summarize at two minutes before noon, Mr. Chairman, the infrastructure is in place, but some modification is required. We are very pleased with the two-year report. We think it is extremely comprehensive and really helps us focus on that desired state.

The culture is changing, it needs more changing, but I think the steamroller is moving and I don't think it is going to stop either in industry or in FDA.

The desired state is on the horizon, we are starting to see it in little bits at manufacturing sites and in research and development sites, you are starting to see the desired state coming to fruition, and I think it is not as far away as some might think.

Thank you.

DR. KIBBE: Thank you. I see by the clock on the wall that we are in plenty of time to actually get up and go to lunch. We have no

individuals who seek time during the open forum, so that we will return and at 1 o'clock we can entertain questions and comments about all of the speakers that we have heard prior to lunch break, and then we can jump right into the information and presentations in the second half of the day.

I know that there are some members of the committee who need to get out of here by 3:30 or 4:00 and we are going to try out best to make sure that the bulk of the work is done before they have to leave, and I appreciate your attendance.

[Whereupon, at 12:00 noon, the proceedings were recessed, to be resumed at 1:00 p.m.]

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

[1:00 p.m.]

DR. KIBBE: I see by the clock on the wall that we should be turning on our equipment, so we can start recording the wonderful brilliance that is coming forth from these meetings.

We agreed before we went to lunch that we would spend some time responding to this morning's activities and give an opportunity for those with extensive comments and questions to discuss the issues, and I know, Nozer, you are ready.

Committee Discussion and Recommendations

DR. SINGPURWALLA: This is to Ajaz. Would you like to sit down while I ask the questions, or would you like to stand? You will stay here.

DR. KIBBE: It's safer, you are further away over there.

DR. SINGPURWALLA: Anyway, I enjoyed your presentation. The ideas again are visionary and stimulating, and the comments I want to make are purely to improve upon what I think is something positive.

The first question I want to ask you is a particular viewgraph that you put up in which you said the future definitions of quality should be probabilistic in nature. This is a comment attributed to Janet Woodcock, although I am pretty sure you may have had the thought.

What do you mean by that? I subscribe to the view, but I would like to see what you want to say to it.

DR. HUSSAIN: I think, in part, that sort of follows a continuum of our discussions at FDA Science Board, and that is the IPAP RS debate also, is we often establish acceptance criteria, and so forth, in a more deterministic type of thinking in the sense of we don't utilize variability as a means of decisionmaking, and our criteria are 75 to 125, that's it, and no unit outside that for a given sample, so it's an outgrowth of that thinking to saying that at one level, to say let's utilize the statistical distribution variability in making decisions.

That is one level of that, but

probabilistic also is linked to the risk-based aspect, and risk is probability for harm and consequences of that, and I think to bring that level of thought into how we approach quality.

DR. SINGPURWALLA: I think this requires much more thought and discussion, but I was curious as to what you had in mind.

On your viewgraph 7, you have those 3-dimensional illustrations of critical parameters, reliability, and life, shelf life is what you had in mind. I could not get the essence of what it is that you were saying there, and the main reason I am raising this particular issue is next time you present it, you may want to rethink as to what it is that you want to communicate, and I didn't get the message.

DR. HUSSAIN: The message was in the sense I think when we often think about shelf life as a point estimate or as a endpoint determination perspective, and so forth, and what I liked about that viewgraph was it brings in the variability, it brings in an understanding of variability from that

context and how variability changes.

So, that was an illustration, and so it provides a means to think about reliability and shelf life together. So, that was the attractiveness of that viewgraph.

DR. SINGPURWALLA: You mean the reliability of a drug?

DR. HUSSAIN: Product.

DR. SINGPURWALLA: Of a product.

DR. HUSSAIN: Yes.

DR. SINGPURWALLA: Well, when we normally talk about reliability of a product, it is the probability of it either living to some life length or doing it or performing satisfactorily or not, so you had a similar notion of reliability in mind?

DR. HUSSAIN: Yes.

DR. SINGPURWALLA: Let me go to your viewgraph No. 24. I want to introduce a new concept based on that viewgraph. This is on page 12. Perhaps I am going to introduce a new buzz word, which you may find attractive in the future. Are you ready?

I think that buzz word may also apply to some of Gerry's presentation. You are talking about substantial, moderate, and minimum as not being probabilistic. You said something to that extent.

DR. HUSSAIN: We haven't defined the probability aspects to that.

DR. SINGPURWALLA: I want to introduce you to the following. You perhaps know that in our presidential debates, President Bush used the word "fuzzy math," and I think now Kerry is talking about "fuzzy calculations." But there is a body of knowledge called "fuzzy sets," and fuzzy sets are those whose boundaries are not sharply defined.

So, the idea of substantial, moderate, and minimum would contribute to what is called a fuzzy set, whose boundaries are not sharply defined, and I think Gerry said something, I forget exactly where, but he was also alluding to a fuzzy set.

Now, what I am recommending to the FDA and to the drug industry and whoever else is listening, that the notion of fuzzy sets may be very useful

here, particularly with your nasal sprays thresholds, with the idea of a threshold. You cannot have a precise threshold. You cannot say that if something is more than 4 inches, it is good, and if it is less than 4 inches, it is bad. The boundary is fuzzy.

There are ways by which you can endow probabilities on fuzzy sets, and I would like to alert you to that particular body of knowledge, and I would like to alert you to looking into it as a possible venue for the kind of problems that you are working on.

This is very recent, very new. The idea of fuzzy sets has been around. Control engineers use it, but to make it precise, and to endow probabilities on it is something very, very new, and the last issue of the Journal of the American Statistical Association has a paper with discussion on that particular topic. I urge you to look at it.

The last comment, and this is a comment, on your last slide, on immediate education needs.

First, I want to say what else you need into this package. You really don't need introduction to statistical quality control. What you need is introduction to statistical process control, because when you take quality control, it goes back to acceptance sampling, and you are really interested in a process.

You say you should understand variability. I think the point is if you understand variability, variability goes away. Once you understand it, you know what to do with it, and therefore it vanishes.

What you really need as far as an educational component is some training and appreciation of what do we mean by uncertainty, and how do you work with uncertainty. I think that is an important component. Once that is understood, all other issues, process control, biostatistics, non-biostatistics, all those become very clear.

The last question is how do you plan to implement this immediate education needs, what are you going to do, hold workshops?

DR. HUSSAIN: No, I think we have

different mechanisms to sort of training. We actually have formal training programs that actually go on, on a regular basis at a training--we used to have what I think we called staff college. There are aspects of that. There is an Office of Training and Communication, which is thinking of a course on design of experiments, and a whole series of courses which are sort of built in. People can take them whenever they have time, so these are ongoing.

But immediately what we have been focused on is workshops, internal seminar series, and so forth. We are starting in a step-by-step fashion. As we move towards the final guidances, for example, we generally have a training around the guidance. Much of that we also get captured there.

But my thoughts are I think we need a portfolio of courses that are available every quarter or every semester, or whatever, that people can take on a regular basis, so we need a curriculum that is available for our staff whenever they choose to take it, and so forth.

DR. SINGPURWALLA: My reaction to these things, available on a semester-by-semester or quarter-by-quarter is that they fail. What you may want to do is have special courses like this throughout the FDA, not just your organization, provided they agree that this is what is needed, and have them, you know, once, and maybe twice, and then stop, but then require that the people who should need that exposure go.

If you keep it optional, somebody says, well, I know statistics, I know what r-square is, I don't need to take a course. That is where the tragedy is, that everybody thinks they know it. So, I propose that you design something specific and go through that.

Again, I am not volunteering since I made the suggestion.

DR. KIBBE: Do you have a suggestion for a college that they could take all these courses at?

DR. MORRIS: Someplace in Indiana maybe, Notre Dame.

DR. KIBBE: I was hoping for Pennsylvania

myself.

DR. MORRIS: Pennsylvania, okay. Actually, the University of Hawaii I think would be good.

I actually had a couple of comments I think that go across Helen's, Ajaz's, and Jon's talk, but I want to preface it by saying that in the time I have been spending with you all, it occurs to me that there is a lot that is right, right now, with the reviewers and the reviewing process that we don't want to lose. I don't get paid any extra for that, by the way.

In that sense, the idea of a two-tiered approach doesn't really seem to have legs to me. In a sense what we are saying is, is that the reviewers would have to be somehow two tiered, and that is really not the way they review.

What we talked about at the last Manufacturing Subcommittee was the idea that when companies can provide a rationale with supporting data, that that automatically registers as a level of understanding as opposed to when the reviewers

have to develop a rationale based on the data that they have available, but at the end of the day, they are still looking for rationales, still looking for flags in terms of safety and efficacy and rationales.

So, I don't really see that there is a real need for that. I mean we can certainly comment on it, and probably should hear from Paul and Gerry on it.

I have a couple of other comments, but go ahead.

DR. HUSSAIN: No, I think that has been a concern, and this was an extensive topic that we discussed at the London meeting of ICH, especially working group meeting on that. The language we have crafted, I mean that took a long time to craft, to say there won't be any two systems or not tiers at all, in the sense it is a smooth transition.

But the reality is you will have much more varied types of submissions.

DR. MORRIS: Absolutely.

DR. HUSSAIN: But that is managing that, and so forth.

DR. MORRIS: And I agree, but I think in that sense, you know, there were a couple of things. You know, the evaluation of the Pharmaceutical Development Report that you had mentioned, Helen, and really it should create less questions if you assume that most questions come from the lack of a presentation of a rationale, so hopefully, we will realize some efficiencies from that.

Similarly, Ajaz, I think the review of the critical variables and attributes should be improved by the Development Report, the P2 and the CTD, as well.

I guess this point you had made in your presentation, as well, I can't remember if it was Jon or you, Ajaz, but the idea that there are already in industry, the scientific expertise. It is a question of how they are organized and linked in terms of communication.

I think the same is true in the Agency.

There is a good bit that is already in place, that just needs to be wired, and that is really all I had to say.

DR. KIBBE: Melvin, did you have something?

DR. KOCH: I had a comment or question for Jon. It had to do with the new process or actually even the old process in terms of creating, say, a draft or a guidance, and after you go through the legal audit, the public comment, and eventually have a final draft, I am just wondering if there isn't--maybe I should ask the question--is there anything that happens before the final draft in terms of explaining how the comments were used?

I know they all show up on a docket, but I know with the most recent PAT final guidance, there were questions that those who are hoping to use it have, mainly because there is some part of it which seems to refer back to doing things the way they used to be, and there is a little bit of inhibition initially in how to use it.

I am just wondering, in the process, you

mentioned something called a public draft, and if, say, after the public comments are taken, you know, the almost final draft shows up for some quick response.

MR. CLARK: The comment that we receive when--this is true of the old process and true in new, as well--public comments received are treated as if they are FOIable whether they are or not. So, there is a documentation of comments, an indication of how they are collated, and the response to them if they are grouped together as a group or individually depending, that is up to the group whether they group them together or not.

The FOI rules, they shift a little on me, I am not sure what level they are available, but we treat them as though they are. It's a public draft, it was not meant to be any different than the current draft that we now publish. We provide a Notice of Availability in the Federal Register and then it is provided on the web. That draft is what receives the public comments.

What I was referring to, the main crux of

what I wanted to have accomplished here was to involve this body in evaluation of prioritization of guidances in general and where we would need them.

In other areas where we talked about this, it had come up that we needed to have a better way of looking at whether or not we needed a guidance in certain instances, because our methods for doing that now usually involve public workshops, very driven by the FDA, and perhaps we should include some more outside opinion as to where we would need guidance.

DR. KOCH: I guess I was wondering is there a process for revision and/or interpretation of a final guidance?

DR. HUSSAIN: No, I think the policy in a sense, we do not plan to sort of outline how we address the comments, only for regulation changes that is a requirement. For guidances, comments, essentially, we don't share that information.

MR. CLARK: If we receive some indication that there are interpretations of the guidance that

aren't going the way we anticipated, this is a point of having a question and answer associated with that document or with that topic.

DR. KOCH: Right, and it is in that context. Anyway, we maybe could talk at some point in terms of some specifics.

DR. KIBBE: Pat.

DR. DeLUCA: I just want to comment, and I guess I best comment using Ajaz's slide, the cGMP Initiative. It is on page 14. It has been my experience that most times in the pre-IND, pre-AND product development process development, that these is a hesitance at actually getting too innovative or pursuing new things and trying to improve a product with the idea that, oh, well, after it is marketed, then, we will do this, which I don't think in my experience that it happens very often.

So, I like this. It is because you have in the circle here that after you get to improve it, and there is a slot there for continuous improvement and innovation, and I think I may have said this before at previous meetings that I think

even after postmarketing, that there should be vigilance in trying to improve the process, and sometimes you have to try to change both in order to do one or the other.

I am certain, seeing here that the expertise certainly exists in the industry the expertise exists here, and kind of encourage that it looks like the mentality may even be moving in that direction, too.

So, that is something that I would encourage as the desired state, that postmarketing, that there is this effort, continued effort to improve the product and the process.

DR. KIBBE: Gordon, you have a comment.

DR. AMIDON: Yes, I have a comment on two of the slides that Ajaz presented. I mentioned one to you at lunch, Ajaz. The other was--

DR. KIBBE: Just give a page number.

DR. AMIDON: On page 11 in your presentation, the top slide. Interpretation and Optimization of the Dissolution Specifications for a Modified Release Product with an In Vivo-In Vitro

Correlation.

I am not sure what implication the authors were making with the dissolution passed, the bioequivalence passed and the dissolution passed, bioequivalence failed, but my question would be what dissolution did they do.

The impression I had from your presentation was it was suggesting that dissolution was inadequate in predicting bioequivalence, and it obviously wasn't, but that is because they did the wrong test, the dissolution test.

So, this implies to me that we need to really be more specific when we are talking about dissolution, what is the test, did the test reflect what is going on in vivo, because if your in vitro test reflects your in vivo process, that has to predict what is going on. Otherwise, there is magic in between.

DR. HUSSAIN: I think the theme of that paper was twofold in the sense to evaluate--if you have the handout, it is part of that--the team was to evaluate the linkage between in vitro

dissolution and in vivo bioequivalence and how variability or random variability sort of plays into that.

Authors looked at what they call a non-optimal specification and an optimal specification, optimized specification based on in vitro correlation, then essentially simulated with random variability built in, in vitro, as well as in vivo, what is the likelihood of finding failed dissolution, so that has been that analysis.

DR. AMIDON: I didn't mean for you to have to defend the paper, and I will have to take a look at it, but there is something wrong here in my mind at least based on this one slide, because if your in vitro dissolution reflects the in vivo dissolution process, it will predict bioequivalence.

DR. HUSSAIN: No, that is the whole point here in a sense. The point here, all we can do with the current dissolution methodologies are the mean values. We have no idea on the variability. So, once you factor in the variability, then, you

see these aspects. That is the crux of that.

DR. AMIDON: The second comment would be on just the previous page, page 10, at the bottom of the slide, which I did mention to you at lunch. I am confused whether this is a flow chart or an event chart of something.

The very first step, does dissolution significantly affect bioavailability, I mean the answer, I have problem with the answer "No," because I can make a tablet no matter what the drug properties, it will not dissolve and disintegrate, so dissolution always affect bioavailability, it is a matter of how much.

I guess my broad comment, and I will make this again later in my presentation, is that we need more research on dissolution particularly in vitro to in vivo. That is where we have the big gap in our scientific understanding today.

DR. HUSSAIN: I think this is an ICH Q6A decision tree, and now looking back after years of this, I do want to give credit to Professor Nozer Singpurwalla that he really pointed out this is an

event tree, not a decision tree, and I actually before that had not paid attention to that fact.

Now, when we look at it after years, some of the questions really don't make sense.

DR. KIBBE: Michael.

DR. KORCZNSKI: This is just a comment related to the past two days of discussion. I think we really heard some excellent data being generated from the FDA labs, and I might add, after spending a number of years in the industry, I wish some of my retired colleagues could have heard the discussion. I think they would have marveled at the progress being made scientifically.

A thought comes to mind. I think this is a very significant question. I have tried to distill a significant thought here. Can innovative drugs, as a result of where we are going and the data we are seeing, eventually be reduced in scope relative to clinical trials and without a loss of patient safety or efficacy?

Just to kind of encapsulate that, if, indeed, you do have some very excellent innovative

types of assays at the preclinical level, such that they perhaps might even mitigate to some degree or reduce Phase I studies, because they are so thorough and better predictors, and then if you got to that stage, could there be a consideration of collapsing Phase I and Phase II clinicals into one clinical trial basically, then, with all the data that we saw from the ICSAS staff, the computerized data, is it possible in some way to network with sponsor companies, such that more drugs could probably be placed in an orphan drug clinical pathway as opposed to the current conventional Phase III.

So, long term, there are some real opportunities, I think, in condensing and collapsing that costly and lengthy clinical trial procedure, and the data to a large extent that is being collected.

Just another two items. One, we talked about innovative drugs. I think what is going to be important, this is kind of futuristic, would be the identification of target sites for disease

states, and very important with the development of these nanomolecules and small peptides will be the delivery systems. What will be the micro delivery system to the host site especially as we talk about gene therapy?

So, the development of that technology has to occur in concert with the development of the molecules, so we are going to have the molecules and not the means to deliver to disease state host sites.

So, that is just an encapsulation. Thank you.

DR. HUSSAIN: On the last point, I think there has been an amazing growth in that particular area, vehicles, nanovehicles, nanodrug delivery systems, and so forth, and we hope to publish a paper soon on the topic of dendrimers and then how dendrimers can sort of shrink promers [ph], and so forth, so there has been wonderful progress even on that side, on the delivery part of it.

DR. KIBBE: Anybody else? Okay. So, we kind of beat that into the ground, and we got that

under control.

We need to move forward. I see that Lawrence is getting ready to go. He has two sets of presentations, and he agreed that if we would just do exactly what he says in the first set of presentations, he would be really fast on the second set.

Pharmaceutical Equivalence and Bioequivalence of Generic Drugs

The Concept and Criteria of BioINequivalence

Concept of BioINequivalence

DR. YU: Good afternoon. This afternoon we have to deal with two topics. One is follow-up topics which we have presented this committee six months ago, and a second topic, introduction topic, is called Bioequivalence of Locally Acting GI Drugs.

Let me go through the first topics of bioINequivalence, concept and definition, which this topic, as I said, was presented to you six months ago on exactly April 14, 2004.

The bioavailability is defined as the rate

and extent of drug absorption. Regularly, we use the Cmax as a surrogate for the rate absorption and the AUC, all to the exact area under the curve used for the extent of the drug absorption.

So, the bioequivalence is defined as absence of a significant difference in the rate and extent absorption, and many other things, for example, become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. So, this is basically the CFR definition.

With bioequivalence, we usually use 90 percent confidence interval for AUC or the extent of absorption, or Cmax rate of absorption between 80 and 125 percent.

The passing bioequivalence criteria or confidence interval allows market access. Certainly, we have to, for example, generic firm have to meet other quality standards. If you pass the confidence interval, or we call the bioequivalence for generics, this means the generic

approvals, for innovators, this means demonstrated to be marketed formulation to be equivalent to clinical formulation.

Those concepts are well understood, well developed, widely used.

The question remains why do we need to define bioINequivalence? It is because FDA receives studies, as we discussed six months ago, receives studies that attempt to reverse a previous finding of bioequivalence, in other words, companies, whether innovator companies or generic companies out there, to conduct a study, say, the generic products or products on the market, in fact, is a bioINequivalent.

The bioINequivalent definition is not very well defined. In many cases, to be scientific term, those studies actually should be defined as failed to demonstrate bioequivalence to be exact. That is part of reason when you define the criteria of a bioINequivalence, when you define the concept and criteria of bioINequivalence.

The question certainly, what should

bioINequivalence mean? Bioequivalence leads to market access, bioINequivalence leads to market exclusion. That is what bioequivalence/bioINequivalence basically means.

Now, come back to say look at the results, what does it specifically mean when I said failed to demonstrate bioequivalence, failed to demonstrate bioINequivalence, bioequivalence or bioINequivalence, those concepts.

In the center, the top one is demonstrate bioequivalence just because the confidence interval for this study is within the bioequivalence interval of 80 to 125 percent.

The bottom one is demonstrated bioINequivalence, I use BIE here, it stands for bioINequivalence. Now, the middle one, basically, the left side or right side, we have fail to demonstrate bioINequivalence and fail to demonstrate bioequivalence. This basically is because neither, whether either outside of the confidence interval, outside of bioequivalence interval, 80 to 125 percent or not completely

inside.

Now, since the April discussion, I received several phone calls and also we had a discussion within FDA with my colleagues, some question came back that by definition of bioINequivalence may be too far. Some people suggest maybe use mean of the point estimate, confidence interval, while the suggestion was that if you use the point estimate or mean ratio outside or above 125 percent, it should be defined as bioINequivalence.

Now, certainly this makes a lot of sense. However, if we look at it deeper, statistically, it is not. Let's look at an example here. The top one, obviously, it failed to demonstrate bioINequivalence. Now, failed to demonstrate bioINequivalence could have been for many reasons. One of the reasons you would think is not enough subjects, for example theoretically, they should have used 100 subjects or 50 subjects, and this study only used 10 subjects.

Because of the small number of subjects,

it makes the confidence interval of the final results much wider, therefore, end up you have a failed to demonstrate bioINequivalence. We see we cannot use this result, failed to demonstrate bioINequivalence as definitive answer, is because if you use large number of subjects, there is two possibilities as you can see here.

Could be bioINequivalence completely below the 80, outside of the bioequivalence confidence, either below 80 or above 125 percent.

There is another possibility that even though the study, this is a small number of subjects study shows bioINequivalence, in reality, they could be bioequivalent, as you show here on the left side, right side or left side. So, the right side one is because once you use large numbers of subjects, could give you a definitive answer, you end up even though the study itself fails to show bioINequivalence, but at the end you have two outcomes, and that is the power that could be demonstrated bioINequivalence or demonstrated bioequivalence.

That is part of the reason we say we may not be able to use these results to have a definitive answer to make regulatory decisions.

The objective is the same which we were discussing back to April 14th, to develop a bioINequivalence criteria that are scientifically sound, statistically valid, fair to all parties, and easy to use.

I want to remind you that the comments or conclusion draws back to the last discussion. The first question, back to April 14th: Does the ACPS agree with the distinction between demonstrating bioINequivalence and failure to demonstrate bioequivalence?

The answer was yes. That was the conclusion reached back to April 14, 2004.

The second question: Does the ACPS recommend a preferred method for evaluating the three pharmacokinetic endpoints for bioINequivalence?

There are many sub-questions. Here are the comments which were discussed.

The committee agreed on a general understanding of bioINequivalence to move forward by recognizing this is not a simple matter. In addition, the members felt that there is an important concept, especially now it applies to entire regulatory scenario. There was no consensus at this point as to a final criteria pertaining to the three pharmacokinetic endpoints.

We will present you today our recommendations based on those discussions and hope we can follow the comments or discussion.

DR. MEYER: Could we ask a question before we get confused with statistics?

DR. KIBBE: Okay, great. Why don't we ask the question before we get statistical.

DR. MEYER: I like to approach things in a very simple manner. If you could get slide 7 back, Lawrence.

It strikes me that you are trying to use phraseology to fit a subsequent statistical analysis, and I am wondering if there isn't a simpler way to go about it. I am kind of, of the

school that you are either pregnant or you are not, and if you haven't taken the test yet, you can't say. So, that is basically where I am going to go.

I am going to number these 1, 2, 3, 4, 5. I think we can all agree that No. 1 is bioequivalent, and No. 4 and 5 are bioINequivalent, just as you have shown.

DR. YU: Yes.

DR. MEYER: I say No. 2 is bioINequivalent, not failed to demonstrate bioequivalence, the pregnancy/non-pregnancy thing. I say that because the mean is well outside 80 percent, and increasing the numbers may shift the mean one way or the other. You shifted it, of course, to the left to make it worse.

I would say maybe it will stay the same. All I know is that the means are terrible, and the confidence limit kind of extends over to acceptable range, but in my view, if somebody came to me with that data and said I ran the study on 40 subjects, should I do 80, I would say no, reformulate.

If they came to me with a confidence level

that lopped that over, I would say, yeah, do an added number.

So, I think the N problem, which could expand confidence limits, can be solved by requiring anyone that dose a bioINequivalence study to fix their N at the same as the person that got the approved ANDA. So, if it took Teva 485 subjects to do their study, then, I think Pfizer ought to do 485 subjects if they are going to try to prove that Teva is no longer bioequivalent for some reason.

No. 3, I would say that fails to demonstrate bioequivalence by the current standards, but it also fails to demonstrate bioINequivalence, because the means are well below 125. That is a wash.

You can't tell one way or the other, therefore, whoever is doing the study can't make a claim of bioINequivalence, because there is ambiguity in the data. That is a much simpler approach than trying to come up with a new metric of 3 parameters or 1 parameter or what have you.

DR YU: Indeed, Marvin, you have excellent questions. That is true, I guess, we have too many discussions on this topic.

Well, come back to your question, is that does fail to demonstrate bioINequivalence, top, No. 2, is actually demonstrated bioINequivalence here, that is the question.

Indeed, you point out it probably could be bioINequivalence if the sponsors, whoever conduct the study, you have sufficient power, was sufficient in number of subjects.

I guess the question comes back under this scenario, that for top one, which is clear, demonstrate bioequivalence, and the bottom one is clear, demonstrate bioINequivalence, however, for No. 2 or No. 3, this does not necessarily--especially for No. 2--if we receive the data, this does not necessarily suggest, we are not going to take any action whether or not you look at it, simply because you fail to show bioINequivalence, therefore, we are not going to take a look at it, we are not going to take any

action, that is not the case.

Certainly, this case, if you submit it to the Agency, and the study is well conducted, well powered, we have to look at all of the scenario and then to draw a scientific decision, or I guess what I am saying is top 1, and top 4 and top 5 give us definitive answer, top 2 and top 3, we have to look at it case by case. We cannot draw very decisive conclusive decisions is part of the reason you have assumption here, you have a sufficient number of subjects.

If you don't use a sufficient number of subjects, say, you only use 1 or 2 subjects, certainly, we were not able to say you have demonstrated.

I hope I answered your question. I guess we answer your "if" questions.

DR. MEYER: How about fixing the N at the same as the ANDA submission used?

DR. YU: That is one of the options, yes.

DR. KIBBE: You are responding to a question that I don't think the Agency is asking.

You are responding to a question that a sponsor of one of those studies would ask in order to get the study to do what it wants to do.

Then, you are saying, well, the Agency should say if they did this, then, they probably would show this and what should we do about that. The difficulty for me in this whole scenario is that the failure to demonstrate bioequivalency doesn't necessarily prove bioINequivalency, and if a product is already on the market because it has a bioequivalency approval, what level of information do we need to reverse that decision.

I agree with Lawrence, those two in the middle wouldn't justify in my mind as a regulator a change in the previous decision, whatever it was. Okay?

DR. MEYER: If the orange one, No. 3, was done under the same conditions as the ANDA holder.

DR. KIBBE: If it was done under the same conditions as the ANDA holder, I wouldn't reverse my decision on anything.

DR. MEYER: That is an exaggeration

perhaps because let's say it's 127, you can't get real excited about that. No, it would have to be 125, but let's say it was 145.

DR. KIBBE: What I am saying is we already have a product that passed once.

DR. MEYER: Right.

DR. KIBBE: That study doesn't help me decide to reverse that decision.

DR. MEYER: The product has changed. Remember, Gary Levy published The Clay Feet of Bioavailability or Bioequivalence Testing. You do it once on a hand-picked lot against one lot of the innovator product, a fresh lot of yours, and one you have selected maybe out of 12 of theirs, and then somebody else comes along with an older lot of theirs or vice versa, and no longer are you bioequivalent.

DR. KIBBE: I understand the argument. I am just saying that, as a regulator, I wouldn't change anything I have got on the books based on 1, 2, 3. Okay?

DR. YU: I guess I will make one more

comment. When you conduct bioequivalence studies, you look at availability, you look at the power, you look at the subject. You are basically always saying here that the bioequivalence criteria is 80 to 1 to 25 percent. Agency never defines how many subjects you use. You could have used 24, 48, 96, 500, for example, for clinical endpoint studies.

So, when you define the number of subjects, then the confidence interval could be variable, one way or another. You define one, and you have another criteria.

I think that for the bioequivalence criteria, we define the confidence interval instead of define the number of subjects.

DR. KIBBE: Go ahead, Nozer. We are having a lot of fun here.

DR. SINGPURWALLA: I think it is always fun when committee members disagree, but something bothers me about this whole concept.

DR. YU: That was not the--

DR. SINGPURWALLA: That was not the question, I understand.

DR. YU: That was not the question.

DR. SINGPURWALLA: I understand, that was not the question.

DR. YU: If we don't want to live with it, I guess the decision will have to be made.

DR. SINGPURWALLA: I am sorry, my comment here is you are building a castle on sand, I think this whole idea--

DR. KIBBE: Or clay, right?

DR. SINGPURWALLA: Whatever you want to use, it's a castle that cannot hold up. What you have done is you looked at Cmax and you looked at AUC, and if the Cmax and AUC are not significantly different, you say there is bioequivalence. Not true? What is it then?

DR. KIBBE: If you are going to give an answer, Don, you might as well get on a microphone.

MR. SHERMAN: Lawrence showed a quote from the regulations on the definition of bioequivalence, and it said rate do not show a significant difference. The word "significant" in that sentence does not mean statistically

significant, it means significant the way the word is used in the English language, substantial, important.

DR. SINGPURWALLA: Then, my comment becomes even more acute. The whole thing should be relooked, revisited, because I kind of agree with Lawrence about those two, and I agree with our chairman about the two middle ones as demonstrating failure to demonstrate, then demonstrating. I mean I wouldn't change anything, but I think the whole concept of doing all this through this particular vehicle of setting confidence limits and looking at the little tail falls here or there seems completely capricious to me, and you may want to revisit this whole topic.

DR. KIBBE: We have been revisiting this since 1970 at least.

DR. SINGPURWALLA: I was not there. Change the paradigm.

DR. KIBBE: We are not revisiting the paradigm.

MR. SHERMAN: I just want to correct the

notion that you look at Cmax and AUC and you approve products as inequivalent if there is not statistically significantly difference. That hasn't been true for decades.

DR. SINGPURWALLA: So, it has been nonsense for decades.

MR. SHERMAN: You are entitled to your opinion, sir.

DR. YU: We will move on to the next topic. Thank you.

Criteria of BioINequivalence

DR. LI: Good afternoon. My name is Qian Li. I am from Office of Biostatistics in CDER, FDA. I am going to present a statistical criteria for evaluating bioINequivalence using multiple endpoints. I know there have been citing for using one endpoint, but I decided to move on to talk about multiple endpoints.

Before I start to talk about the criteria, I would like first to discuss the question why we need to use multiple PK endpoints to assess bioINequivalence.

To answer this question, we need to understand that for systematically delivered drug product, bioequivalence established by comparing the rate and extent of drug absorptions. The rate and extent are usually represented by Cmax, AUCt, and AUCinfinity.

In statistical terms, Cmax, AUCt and AUCinfinity, I refer to as PK endpoints. For bioequivalence assessment in generic drug approval, it has evolved to use AUCt, AUCinfinity, and Cmax. As Lawrence has mentioned before, that you have to prove that 0 to 3 PK endpoints to be equivalent in order for the generic drug product to have market access.

Now, for bioINequivalence, it can be established if one of the PK endpoints are inequivalent in truth.

Now, in reality, we do not know the truth, so we have to perform statistical analysis to test all the PK endpoints. That is why we need to assess multiple PK endpoints. I hope this is clear to everybody now.

Now, this is the outline of my presentation. I will give a brief review on the criteria for bioINequivalence using one PK endpoint and then present strategies for assessing bioINequivalence using three PK endpoints, and I will discuss available approaches and then present power comparisons of those approaches.

Then, I will discuss FDA's recommendation of using the three PK endpoints in assessing bioINequivalence.

Now, let's first look at definition of bioequivalence and the inequivalence using one PK endpoint.

We use the ratio of geometric means Mu T/MuR to define bioequivalence and INequivalence. Mu T represent the geometric mean of the test product, and the Mu R is the geometric mean of the reference product.

The bioequivalence is true when the ratio is between 80 percent and 125 percent. We call this bioequivalence interval. Outside this bioequivalence interval is defined as

bioINequivalence region.

Now, to test the bioINequivalence, the null hypothesis is the bioequivalence interval. The alternative is the bioINequivalence regions. Similar to bioequivalence test, we will perform two, 1-sided test, as well for bioINequivalence assessment.

The null hypothesis for 1-sided test is to have the ratio reached and equal to 80 percent, and the alternative is less than 80 percent. There is another test that now is less than or equal to 125 percent, and the alternative is driven 125 percent.

We can claim bioINequivalence if one of the two nulls is rejected. We perform the test on the significance level of 0.05. Now, this is the equivalent to form 2-sided 90 percent confidence intervals.

The criteria to claim bioINequivalence is when the 2-sided 95 percent confidence interval lies completely outside the bioequivalence interval.

I would like to remind everybody here that

using 2-sided 90 percent confidence interval for bioINequivalence test, the error rate is not always protected at 5 percent level. This is different from bioequivalence test.

If we have a reasonable conducted study, say, it's a 2-sequence and a 2-way crossover design, and the subject is more than 20, and the within-subject standard deviation is less than 0.7, then, we can safely control the error rate to 5 percent, however, if the subject sample size is less than 20, we have large variance for the test statistics, then, the error rate may not always be controlled at 5 percent. In this case, we might have to consider to use 2-sided 95 percent interval.

Let's move on to the definition of the bioequivalence and the inequivalence using three PK endpoints. As mentioned before, the three PK endpoints is Cmax, AUCt, and AUCinfinity.

The definition of bioequivalence is the cubic region in this 3-dimensional diagram. Outside this cubic region will be the

bioINequivalence region.

For the criteria for bioequivalence assessment using three PK endpoints is to require all 3, 2-sided 90 percent confidence interval for the ratios of our geometric means has to be reaching the bioequivalence limit.

Now, the error rate of wrongfully rejecting bioequivalence using this criteria is protected at 5 percent level.

Now, for bioINequivalence assessment using three endpoints, we are looking for a strategy that can control the error rate of wrongfully rejecting bioequivalence at a rate of 5 percent.

Also, we want to control the error rate under all correlation structures because we do not know the correlation structure of the three PK endpoints.

Now, to develop those strategies, we assume the variances of test statistics are not large.

Now, there is a common misconception when assessing bioINequivalence. The common

misconception is that to claim bioINequivalence, when one of the three PK endpoints satisfies the bioequivalence criteria, which is the 2-sided 90 percent confidence interval is outside of the bioequivalence interval.

Now, we will not accept this kind of approach to assess bioINequivalence because it will inflate error rate of wrongfully rejecting bioequivalence. The error rate can be up to 15 percent if three endpoints are independent, can be about 8 percent if the three endpoints are highly correlated. We consider that approach is quite liberal.

Now, people may want to think about we can use quite tough criteria, which is to claim bioINequivalence if all the three PK endpoints satisfy the bioINequivalence criterion, which is 2-sided 90 percent confidence interval outside of the bioequivalence interval.

These tough criteria will tightly control the error rate under all correlation structures, however, it won't provide good power to demonstrate

bioINequivalence, therefore, we are not recommending to use this criteria either.

What we would like to recommend are the following strategies. The first strategy we present here is to pre-specify one of the three PK endpoints for bioINequivalence test. For example, if you decided to use AUCt to test the bioINequivalence, then, you can perform analysis on this endpoint only, ignore the other two.

The requirement for this strategy is that you have to pre-specify this endpoint in your study protocol. Otherwise, you could end up switching endpoints, which may inflate error rate, which we don't like to see that.

Now, this strategy is ideal for situations when one knows that one specific PK endpoint is more likely to show bioINequivalence than others, but it may have poor power if you misspecify the endpoint.

Another strategy we would like to recommend is called Bonferroni corrections. There are many versions of Bonferroni corrections. One

example of using Bonferroni correction is to use a 2-sided 96.7 percent confidence intervals for three endpoints instead of 90 percent confidence interval.

If one of the three 96.7 percent confidence interval fall in the bioINequivalence regions, we will say the bioINequivalence is demonstrated.

This strategy is ideal for scenarios when one knows that one PK endpoint is more likely to demonstrate bioINequivalence than others, but do not believe that all the endpoints have good power to demonstrate bioINequivalence.

Another strategy we would like to discuss here is to use three confidence intervals with different lengths. This can be considered a variation to the approach that requires all the three endpoints to satisfy the bioINequivalence, which is the very tough criteria. This criteria will control the error rate no more than 5 percent.

One example of this criteria is to use 94 percent confidence interval, 98 and 96 percent

confidence interval for the three endpoints instead of all three, 90 percent confidence intervals.

This approach is ideal for situations when one has no idea which PK endpoint has the best power, but you know that all the three endpoints could show bioINequivalence.

To support what we have discussed for the three strategies, I would like to show you some power examples for several scenarios for the three strategies.

We calculated power under two correlation structures. The first scenario is that only one endpoint has good power to demonstrate bioINequivalence. One example is that AUCt has only 5 percent power, AUCinfinity has 20 percent power, and Cmax has the best power, which is 90 percent.

In this case, if we choose pre-specified strategy, we could have a power between 5 percent and 90 percent, so this example clearly shows that if you know Cmax is the endpoint that could give you the best power to demonstrate bioINequivalence,

then, you should choose the strategy to pre-specify Cmax in your protocol.

In this example, Bonferroni correction also can give you quite a robust power, but the varying confidence interval approach is not as good as the other two approach.

Now, for second scenario, which is all three endpoints have reasonable power to show bioINequivalence. Now, here, one example is AUCt has 60 percent power, AUCinfinity has 70 percent power, and Cmax has 80 percent power.

Now, the per-specified approach give you 60 to 80 percent power. The Bonferroni correction will give you about 64 to 72 percent power, and under the varying confidence interval approach, we will give you about 70 percent power.

So, in this case, if you feel that all three endpoints could demonstrate bioINequivalence, then, varying confidence interval approach might be a good choice.

This scenario is that all three endpoints have equal power. All has 80 percent power. In

this case, if you know exactly that all has 80 percent power, then, you can choose pre-specified approach, but this is probably unlikely known to us before we do the experiment.

Now, in this approach, Bonferroni correction will give you decent power, but varying confidence interval will give you probably the best power if you don't know that all the endpoints has equal power.

This leads to the summary of our recommendations on using three PK endpoints for assessing bioINequivalence. When one knows which endpoint is more likely to show bioINequivalence, Strategy I should be used, which is to pre-specify the endpoint in study protocols and use the endpoint to test bioINequivalence. For this approach, you should use a two-sided 90 percent confidence interval.

When one knows that one endpoint may have good power, but do not believe that all of them, all of the endpoints have good power, then, we suggest to use Strategy II, which is the Bonferroni

correction.

One example of Bonferroni correction is to use a two-sided, 96.7 percent confidence interval. If you believe that all three endpoints could have reasonable power to show bioINequivalence, then, Strategy III should be recommended.

The example of Strategy III is to use 94 percent and 98 and 65 percent confidence intervals.

Thank you.

DR. KIBBE: Questions? Go ahead.

Committee Discussion and Recommendations

DR. GLOFF: Art suggested over lunch that I say something this afternoon to earn my keep here. I have a question, it is probably an uninformed question, so I apologize for that.

Is there any provision in all this to look at the results for the reference product relative to the results for the reference product that were obtained either by the company that submitted the ANDA in the first place or prior results submitted by the holder of the NDA?

DR. LI: To my knowledge, I don't think

so. I don't know.

DR. YU: I guess the bioequivalence confidence is defined 88 to 125 percent, so that is the criteria we use. Under certain circumstances, when, for example, the variability is significantly high, we will get clinical studies. We will look at the availability, how much they impact the confidence interval, but the criteria still remains 80 to 125 percent.

DR. GLOFF: Well, I am sure you probably have thought of why I am asking that question. A prior speaker made the comment that when a generic is being developed and submitted, that they could hand-pick the lot that the generic company uses to compare to and hand-pick the lot of the innovator product.

I am sitting here thinking, well, why couldn't the innovator company do the exact same thing to try to demonstrate that the two were bioINequivalent or were not bioequivalent, and I don't know if the Agency came to that conclusion, what they would then do for sure, but I am

concerned about that, that you do that, and then where are you.

DR. YU: I guess the information for bioavailability, bioequivalence, as clinical pharmacology sections, it is available in the public domain, so any sponsors, any companies out there, you can request, go through Freedom of Information and get those information from FDA before you conduct any studies.

DR. KIBBE: Go ahead, Ajaz.

DR. HUSSAIN: I think the question that is being asked is how do we relate one study finding to what happened in the previous one. I mean that is the fundamental question.

We actually don't do that. We often don't do that. But I think that is an important point, and I have tried to look across different ANDA submissions, especially when Gordon Amidon was at FDA and we did a lot of the data mining for our BCS classification, we looked at all that.

I think there is value to that, but often we find that absolute numbers that you see in terms

of percentages is fine, but the absolute values that you see depends on the assay variability, and so forth, differences, and so forth.

But I think no matter what you see, one study, the second study being done to show bioINequivalence in the first study, there is an aspect of selecting the thing, and that has been discussed as Marvin said, profoundly by the father of biopharmaceutics, Garrett Levy, so that is part of the systems.

DR. KIBBE: Jurgen.

DR. VENITZ: I have a question on Slide 11. This is where you were discussing using the three PK parameters and you are commenting that you don't recommend that because there is not adequate power. I would like for you to explain that statement to me.

DR. LI: This criterion to require all three endpoints to show bioINequivalence, the bioINequivalence criteria for one single endpoint is 2-sided 90 percent confidence outside of the bioequivalence region.

So, if you remember our previous talk, we showed a power of showing bioINequivalence. It is pretty hard to show bioINequivalence for one endpoint.

DR. VENITZ: How do you define power?

DR. LI: Power is the probability to show bioINequivalence if bioINequivalence is true.

DR. VENITZ: So, you are ignoring the fact that you have a previous study that says the two products are bioequivalent, in other words, your power is only defined post hoc after this single experiment that you are trying to address?

DR. LI: No, the power is not defined by the experiment. It is a probability which you don't know actually, you do not know.

DR. VENITZ: But you do have prior information that two products are bioequivalent, right?

DR. LI: Right, you could have. What has driven power is how far the bioINequivalence away from the bioequivalence interval. The further away from bioequivalence interval, you have back-up

power, and also it depends on how many sample size you use, which is sample size basically reduce the variability.

DR. VENITZ: But don't you then ignore, as I said before, in your power, the way you define power, the fact that you have prior information? You are just basing it on a single experiment. You already have an accepted study that says those two products are bioequivalent, and now you are saying, well, I need more power to show that they are bioINequivalent. Isn't that kind of a contradiction?

DR. LI: I didn't see the contradiction. What I am trying to explain to you, that to use three endpoint to show bioINequivalence--

DR. VENITZ: Is hard.

DR. LI: --is harder.

DR. VENITZ: Right.

DR. LI: Because the power is lower.

DR. VENITZ: And I am saying you already have evidence to suggest that they are bioequivalent, shouldn't it be harder.

DR. LI: Well, no, if the drug is truly bioINequivalence, if you design your study properly, you should have good power to show that, but if you choose this criteria, you probably won't have good power. You could choose the better criteria that give you better power.

DR. KIBBE: You are beaten.

DR. VENITZ: Okay.

DR. KIBBE: She is talking about statistical power of the individual study presented to her.

DR. VENITZ: I am talking about the overall power to rule whether something is bioequivalent or not in the totality of the information that you have, not just the specific study, which is what you are talking about. You are talking about a specific study where you look at the three parameters individually, you correct it or all three of them.

DR. YU: I guess, Jurgen, you are absolutely correct. Actually, we have many, many debates and discussions, Qian knows that, talk

about when the statistic versus you have a prior knowledge about bioequivalence or bioINequivalence or quality.

Certainly, what we are trying to address here is actually, you have five potential options. One of the options is you have no prior knowledge whatsoever. That is one of them we have to present as a complete picture, we are not recommending this.

One of the options, we say--all the option scenario out there, I guess, one of the scenarios, in your mind, you have a prior knowledge that is impossible, but for the completion of the picture, that was presented.

DR. KIBBE: We have got Ken and then Paul, Nozer, and me, and Marvin.

DR. MORRIS: A quick comment. Irrespective of whether this is innovator or generic, I think the fact that you can hand-pick lots that are this different says more about the process that is being used to make our products than it does our testing for bioINequivalence. I

think this was Levy's point either directly or indirectly is that it is probably more to the point that we need to control our processes to the point where Jurgen's observation becomes the rule in a sense.

DR. KIBBE: Paul.

DR. FACKLER: Part of the problem, I think is we are trying to do an exact science here where the whole issue is so variable, it is out of our control. If we run the same study in the same set of subjects twice, we will get two different results, the same drug product, the same people, and it's different.

The variability is just unmanageable, so a generic company will take a lot of innovator product and a lot of generic product and run it in a certain number of subjects, and that number is calculated to give us 80 percent power. Four out of five times, those products will statistically appear to be bioequivalent, and one out of five times they won't, they are not bioequivalent.

It's statistics, and we should not spend

too much time trying to get an exact measurement here of what bioequivalence is, nor what bioINequivalence is. I think the question is really when is a product not going to perform for the patient who is taking it, and we have arbitrarily said 80 to 125 works, and there is some anecdotal evidence over the last 25 years that the generic products on the market work.

So, I would just caution the committee to be careful defining when you would want to pull one of those products off the market.

DR. KIBBE: Nozer.

DR. SINGPURWALLA: Well, first is I think you have done a very thorough, detailed analysis given a badly defined problem. You have done very well. Thank you.

Now, I am going to comment. I am going to ask you two questions. You have this AUCt. How do you pick the t?

DR. LI: The t is the time point that you can still identify the drug concentration in your blood.

DR. SINGPURWALLA: It's the last.

Is it possible that for one t, you will arrive at one decision, and for another t, you will arrive at another decision, which goes back to what Paul has been cautioning us about?

DR. LI: Uh-huh.

DR. SINGPURWALLA: That is one comment. The last comment is your last viewgraph. When you say "recommendations," you have three bullets. When one knows this, you do this. When one know this, you do this. When one knows this, you do this.

Well, what do you do when one knows nothing?

DR. LI: Actually, this is a very good point. If you see my example, the 3 example, if you know nothing, actually, Bonferroni correction give you quite reliable robust power even it is not the best power for that situation, but it give you pretty good power, we might recommend this, and actually, this probably will be the default approach for us to review if the sponsor didn't

specify any approach.

DR. SINGPURWALLA: So, maybe you should put a fourth bullet, if you know nothing, do this.

But now let me go back to the main discussion that has been spawned by Carol's question. I think both Jurgen and Ajaz have been dancing around the issue, and not coming out right and saying what is on their mind.

Basically, what is on their mind is if you have prior information, which you do have, what do you do, and really what we should do is not address the problem in the manner in which this is addressed. No criticism intended to you of the way you have done it. You have done it very well.

I think you should formulate this as a problem in making decisions. You either declare bioequivalence or you declare non-bioequivalence, and the declaration of one or the other is a function of what risks it may entail if you make the wrong decision, so that takes care of Paul's argument that there is so much variability.

You make decisions in the face of

variability, so that would recast this whole problem, reformulate it, and readdress it. It's a serious issue, because really, what you are all doing is building a superstructure on something that is not carefully defined.

Thank you.

DR. KIBBE: Marvin, do you want to jump in or do you want me to jump in?

DR. MEYER: Well, let me just comment. In my experience--and there is probably exceptions certainly--if I had to pick a parameter to show bioINequivalence, I would go with Cmax. That tends to be a lot more variable, wider confidence limits, so I think you could probably go a priori with Cmax and use Strategy I if you wanted to do that.

You are saying if I do that, then, the confidence limits has to be totally outside of 80 or 125.

DR. LI: Right, yes.

DR. MEYER: Otherwise, you can't tell perhaps.

DR. LI: Yes, it is exactly the picture

Lawrence showed you before, and if you feel uncomfortable, I think there is a second picture that has failed to show bioINequivalence.

Actually, I would like to come to answer that question from a statistical point of view. You like to see, you know, the picture, if the confidence interval overlap to about bioequivalence interval, which is the second case.

DR. MEYER: I am really more worried about means.

DR. LI: The mean is outside the bioequivalence. Let me tell you about the statistical concerns. If we claim, be clear, this is bioINequivalence, then, you end up to make the error that is a modern FAQ [ph] event, which for statisticians, we do not like to see this happen, and if you have the confidence interval completely outside of the bioequivalence interval, then, we are comfortable that if you would claim this drop is bioINequivalence, we won't make error more than 5 percent.

I know for pregnancy test, you could claim

that lady not pregnant, even 51 percent sure, and you could make a 49 percent error, but for statistical decision, for regulatory decision, we cannot make more than 5 percent error. That is why we define it has to be outside the region.

DR. MEYER: I guess I worry about too much rigor in that. Let's say the point estimate was 60 percent, pretty bad, and the confidence limit, because of high variability, went over onto 80.2 percent.

You have a bioINequivalent product, there is no question about it. You are not going to fix that by anything other than reformulation, but because of variability, you managed to slop that righthand tail over above 80.

DR. LI: What if people tell you the study is conducted using only five subjects, and you see the point estimate is 60 percent, and you have a confidence limit, you know, almost everywhere, can you claim this is bioINequivalence?

DR. MEYER: No, that is why I think you ought to fix N, too, to avoid that kind of an

issue, and maybe even fix the mean must be less than the mean ratio in the ANDA.

DR. LI: If we fix, that will lead to stagnation [?] of bioequivalence and bioINequivalence. Maybe we will fix our approach after the problem is redefined.

DR. YU: I do not see actually any difference. I personally perfectly understand your concern. For example, there are two scenarios we can talk about to this figure, which figure No. 2. One of the scenarios is point estimate is 79, the confidence interval is 78 versus 81. Another scenario is the point estimate is 60, confidence interval is 40 to 80, for example.

Under these two scenarios, from statistical perspective, we cannot give you a definitive answer, however, the first scenario, do you know the drug. Certainly, we can definitely use prior knowledge with respect to safety and efficacy of this drug, and we will make a scientific decision.

The first case, you might have to think

about it, because this drug is still on the market, you are perfectly okay, and you will make a scientific decision on the second case. Obviously, we will not close eyes and say let it go, definitely not, and chance to be pulled to the top of the company is high.

Even the first case, we will inform the company, we will discuss with the company what to do with that case. Certain case, the probability to be pulled is higher. I would not say 100 percent definitely as the first case, that bioINequivalence case, this case, certainly we will take a look at it and discuss it with our clinicians within FDA, discuss it with our sponsors outside of FDA to take a proper action as issues occur.

I hope this answers your question. Thank you.

DR. KIBBE: Let me just throw a few random thoughts in on the table with the intention of keeping us all past our flights, so everybody misses their flight.

First, if a product has already been established as bioequivalent, it has been on the market for a while, and we have a lot of confidence in the product, then, I think to pull the product off the market, we have to make a clear and distinct argument that the product is indeed failing to live up to the criteria that was established for it.

It is hard for me to imagine a product that got on the market with a bioequivalency study where the mean values were, say, 97 percent or 103 percent of the mean, the innovator, and well within the confidence interval, and all of a sudden you are going to find a lot that is going to be a disaster.

However, it is possible. If that is the case, then, you have before you two experiments with opposite results, and in most laboratories that I have been involved with, when you have two experiments with opposite results, everybody looks at each other and says we have got to do it again, we can't just leave it like this.

So, no matter what you do as an agency setting up guideposts for the innovator to come forward with a bioINequivalency study, I think then the Agency says thank you very much for a second piece of information, and we now must resolve the discrepancy, not by trumping their study with your study, or trumping your study with their study, but doing the critical study, which is now the Agency should go out in the marketplace and buy 100 of each of the products off the shelf somewhere, maybe St. Louis, maybe Kansas City, somewhere.

I would be afraid that if we went to Canada, we would get much higher quality products, and we want to stay with the quality level here, and do the third study, and then say, okay, your company did it with whatever biases that might have been involved in the selection to get on the market, and your company did it with whatever biases or not that you had and to show that it was off market, and we did it, and now we have the definitive result, and we have to limit the number of times you can come forward and do this with us.

So, we have done the third study. Otherwise, I think it is really one of those he trumps you, and you trump him, and if they come forward with a bioINequivalency study that seems to pass the criteria, whatever you pick, and I come and give you a second bio study with the product and say, look at that, it really is good, what do you do?

Let them trump and trump and trump, and I know the CROs are all saying oh, shut up, let them do it, because we can do these studies, you know, once a month, it would be okay, but it is not going to get you the final answer.

There is a couple of other things that you might want to keep in the back of your mind. Drugs which are non-linear, are easy to manipulate.

If you do a study with dilantin at 50 milligrams per patient, and you get a bioequivalent result where one is just slightly higher than the other, then, get a group of patients and give them 400 milligrams, and you will run that mean right off the table, and what would be an insignificant

difference at a reasonable therapeutic level would not be a insignificant difference at an elevated or above normal therapeutic level.

There is lots of things we can do, so that if we are going to get into this, I would go with a nice tight bioINequivalent study, and we can argue the value of the statistics, but that can't be the end. That absolutely cannot be the stopping point.

That is just one more piece of data, as Jurgen correctly points out. We already have data, now we have new data, and to resolve it, we have to have an impartial arbiter, and the Agency has to do its own biostuff.

Gordon wants to disagree with me. Go ahead.

DR. MEYER: Actually, I think that is a good idea, but I think that given the resources, that there is no reason that an innovator can't be expected to do a study properly. They will get inspected on the first one anyway, the first bioINequivalence study, they can be inspected on the second one. They are not going to risk their

reputation by messing around with the data, so I don't think the Agency, I mean that would be impractical for the Agency to have to run out and do a confirmatory study.

DR. YU: We come back the April 14th discussion, and I think all of us heard Gary made the presentation back in July that our submissions this year increased 25 percent, and then we talk about risk management, we talk about where we put our resource in, and all we are doing for this bioINequivalence type is Agency have defined the criteria for bioequivalence, we want to define the criteria for bioINequivalence to make a clarification out there.

That's all come back because in the literature, scientific literature, people tend to conduct a bioequivalence study, now the confidence interval is 79 or 126, claim as bioINequivalence.

We say this is not scientifically valid. So that is the whole purpose is wanting to give a clear definition with respect to bioequivalence versus the bioINequivalence, as well as a fail to

demonstrate bioequivalence and a fail to demonstrate bioINequivalence.

Then, from here, you are absolutely correct, when we see a study like that, if we cannot--we are trying to put our resources in the NDA reviews. Just in case this happened, cannot be very clear, there is an ambiguity in the gray area, certainly, Agency will have to put the resource whether we like it or not. I think we agree. Thank you.

DR. KIBBE: Go ahead, Gordon.

DR. AMIDON: I am not going to disagree with you, Art, but the question I have regarding the scenario where a product is bioequivalent and on the market, and another company comes in showing potential bioINequivalencies, has the product changed.

If we had a good dissolution criteria in evaluation, we would have some underlying possible more scientific hypothesis to make rather than run out and test another set of products.

So, I think it comes down to dissolution.

DR. KIBBE: Just so you know, bayesian dissolution.

DR. GLOFF: One quick comment on what Gordon just said. He said has the product changed, and my question would be, and if so, which of the two products has changed. It is not necessarily just the generic.

MR. BUEHLER: Well, Lawrence made a good point, and this is a resource issue for us. We haven't gotten that many challenge studies recently. When we do get them, they are usually out by, like Lawrence said, a little, 127, 79, something like that, but the letters that accompany them are very profound.

They are big public health issues, they are always presented as huge issues, and, of course, we have to look at these, we have to address the issue and resolve the issue because I agree with Gordon, we don't want generic products out there that are bioINequivalent. That is a problem for that particular product, it's a problem for the entire industry to have products where the

American public can't have confidence in those particular products.

We want to know about those products, and we want to know when products are truly bioINequivalent, but we don't want to have to deal with all of these studies that come that are just a hair out one way or a hair out the other.

We like rules in the Office of Generic Drugs, and we are sort of bound by our rules, and however, you know, they are criticized by some statisticians, we do have our 80 to 125 rule, and we stick by that very rigidly, and to not do that would mean a tremendous creep, you know, a tremendous I think lack of confidence in the generic process.

Is 79 okay? Well, you know, sure, okay, 79 is okay. But what about 78, what about 77? You can to down, you can go up, and the next thing you know, you have a confidence interval you can drive trucks through.

So, that is why we are very particular about rules, and in this particular case, you know,

this is what we are trying to get for bioINequivalence, is some kind of a rule that companies won't send these in if they know that we are not going to deal with them.

If they know that our rule is it has got to be this far out or this far over--

DR. KIBBE: Let me ask you a question. The ones that you have gotten, would they have passed this rule that you are putting--

DR. YU: The one we have right now--how many addition we have? Probably 41 additions already back and forth, four or five people involved with the lawyer and the scientist involved. The case we have, we hope we resolve very soon, but this case submitted to us back to '99, I think, submitted again in 2002, and you can see how many resources we are putting in, more than two years already passed.

The issue is this case we are here, the confidence interval is--I have got a lower one--the top one is 126.

DR. KIBBE: And it's Cmax.

DR. YU: It's Cmax.

DR. KIBBE: So Marvin is right.

DR. YU: Oh, it's always Cmax.

DR. KIBBE: Of course, it is. Would this proposed rule have said upfront that you haven't established your case?

DR. YU: Absolutely, yes. You can see that, two people for two years.

DR. VENITZ: Can I make an observation and then give my recommendation? First, I agree with Nozer, we are trying to squeeze a bayesian problem into a frequentist scenario, but given the fact that we have been hearing this time and last time that those are the rules that have been in effect for 20-plus years, that we don't find people dying on the streets, or they might be working actually in terms of providing safe and effective generic products, you are stuck with the system the way it is right now.

So, I way I tried to approach it, not being a statistician, we have a body of evidence to suggest that the generic and the reference product

are bioequivalent. That is the reason why it got approved in the first place.

I assume as part of your review, you are going to look for things that might have changed, creep in either the product or the reference product.

So, now you have a claim being made that seems to contradict that, and then, in my mind, the burden of proof is with the person or the organization that files that claim. So, the burden of proof to me means that it has to be difficult for them to overcome what you already know, so I personally would go with the toughest off your recommendation, and you have excluded my favorite one, which is all three of them have to pass: Cmax, AUCt, and AUCinfinity have to pass, because that is toughest route.

If you can overcome that, then, I think you can argue, well, that is about as much evidence as you need given the fact that you already had pre-existing bioequivalence. Then, you have enough to overrule.

So, I would recommend what you didn't recommend, that all three parameters, all three metrics have to pass in order to conclude bioINequivalence.

DR. KIBBE: What do you recommend, Marvin?

DR. MEYER: I might say I am going to apologize for not being a statistician--I once said pharmaceutical scientists all apologize for not being statisticians, but statisticians don't apologize for anything. I think that probably applies here.

DR. KIBBE: I will let you comment on that later, Nozer.

DR. MEYER: Under Strategy I, Lawrence, prespecify one of the three PK endpoints, and then analyze that. Now, if you do a PK study, you are going to have all three at hand. Why don't you just do Cmax and then do AUC, and then do AUCinfinity, and look at the data? What is the problem with doing that?

DR. YU: Let me explain that first, that the criteria, when we define, statistically

significant or not, is 5 percent of criteria. If below 5 percent, statistically significant; above, it is difficult to say.

For you to not prespecify anything, you conduct a study, the chance to be wrong is higher than 5 percent. In fact, change on one slides, I believe it could be high, like 14 percent.

DR. MEYER: Isn't that if you use all three?

DR. YU: If you use any of three. You don't not prespecify any of them, they are just looking for one. For examples, these are the slides, the error rate could be 14.7 percent. If that is the case, scientific speaking, is too high. Certainly, scientific speaking will look at a case, you just present it and make a scientific decision.

DR. MEYER: But if you pick one and pick the wrong one, you also have a chance of being in error, which isn't in there somewhere.

DR. YU: That is correct. You are absolutely correct, Marvin. Actually, you understand very well in my judgment. If you

prespecify and if you use AUC, the wrong one, you could have a probability power. The power could be 5 percent to 90 percent, however, you just said you have a prior knowledge, so most likely you have probably picked the correct one.

Now, let's put the stack back. Indeed, there is a company out there. Pick the wrong one, but even the wrong one you pick, for example, you pick the Cmax. The case I will talk about is very theoretical.

You pick up a Cmax, but it end up an AUC, you show the confidence interval, for example, 60 to 79. This is certainly the case is, statistically speaking, you do not see, the error could be a lot higher, but this does not mean we are going to close eyes, the Agency will not take an action, probably not, absolutely not.

We certainly will investigate. As we said, we look at a formulation change for both innovator and the generic side. We look at all the scenarios. We will have a bunch of people sitting in the conference for many hours, probably many

meetings, and discuss with many parties and trying to make the best decision for the public.

DR. MEYER: Let me just say that if you pick an area under the curve, you are not getting any information about rate, because area under the curve can be quite independent of rate.

If you pick Cmax, you are getting information about rate and amount, and also information about how different your population is, and lots of that kind of information, because Cmax has bounced all over the place especially when Cmax has also moved around Tmax, and the Tmaxes aren't constant, so your Cmax from one patient is going to be happening at half an hour, and then the next patient's Cmax is going to be happening at one hour, and you are going to have lots of fun.

I really think Jurgen is right, that you need to establish a criteria that looks at all of the three parameters for bioINequivalency, because we look at all three parameters for bioequivalency, and pre-existing information has to be trumped effectively. I still like the idea of doing a

third study.

DR. YU: Thank you.

DR. KIBBE: Nozer, do you want to comment on his statistics?

DR. SINGPURWALLA: Oh, he was absolutely brilliant. I am disappointed he went into pharmacy.

DR. KIBBE: Pat, go ahead.

DR. DeLUCA: In your diagram, Lawrence, you know, to me, there is only one here that demonstrates bioequivalence, the others are not bioequivalent, so however you turned them, the other four are not bioequivalent.

But the question I would ask, in determining that the product was bioequivalent, you need Cmax and area under the curve.

DR. YU: Correct.

DR. DeLUCA: If they came in with just Cmax or just area under the curve, you wouldn't have approved that as being bioequivalent, is that right?

DR. YU: Absolutely.

DR. DeLUCA: So, if they just had one that wouldn't be, you wouldn't approve it if they just had one. So, I can't see why, then, if you are looking at a product that is bioINequivalent, why you can't just use Cmax.

You can just use one of them to me, because they had a pass, both of them, at the start, so if they didn't have both of them, they wouldn't have passed bioequivalence, so why isn't one enough? Why isn't just Cmax enough to show bioINequivalence?

DR. KIBBE: Paul.

DR. FACKLER: Just one quick point. The generic has to pass Cmax, AUC zero to t, and AUC zero to infinity under fasting conditions, under fed conditions, and for capsule beaded products, under sprinkle conditions.

So, for some products, it is nine parameters that need to pass, for others, it is six, and for a relatively small group of products, it is three. I just put that out there for what it is worth.

DR. KIBBE: Marvin.

DR. MEYER: You asked for a recommendation. In the spirit of harmonization, I would suggest that Lawrence's figure there is perfect, that under standard conditions, no monkeying with the confidence limits, not 86, not three different ones, keep our 80 to 125, 90 percent, and declare the two bottom ones bioINequivalent, and therefore bad, and therefore need investigation, and the rest of them are all either unknown or bioequivalent.

DR. YU: Thank you. That is actually what we are recommending.

DR. KIBBE: Anybody else want to jump in on the consensus recommendation wagon?

What do you think, Carol?

DR. GLOFF: I have a question for Marvin. Do you mean that all three parameters need to fall outside?

DR. MEYER: No, this could be any of the three parameters, any one of the three exhibiting either of the two bottom ones, bioINequivalence.

DR. SINGPURWALLA: I would like to make a comment from mathematics. To disprove a theorem, all you need is one counter example, so if you want to show bioINequivalence, all you need is one violation. If you want to show bioequivalence, then, you may have to go and do everything else.

Does that rhyme well with your view, Jurgen?

DR. VENITZ: I am not sure because I still think that the hurdles that you have to overcome to get an approved generic on the market, not just looking at Cmax, I mean the other things as you have heard, and it may just not be a single Cmax, it may be other things.

Given the fact that, as you have heard me talk about earlier this year, the 80 to 125 percent is really an arbitrary goalpost. I do believe that the burden of proof should be high for somebody to get this reversed, to get an approval reversed.

DR. SINGPURWALLA: But the burden of this proof need not be so high.

DR. VENITZ: Think about what

bioequivalence means. It basically means you don't have enough evidence to reject a null hypothesis, to use statistical lingo. You are basically trying to prove the impossible. You can never prove that something is equal. So, you are just bounding. You are saying, in my mind, I put arbitrary bounds on, and say, well, as long as it fits those bounds, we consider it to be bioequivalent.

So, to disprove that, I think you have to disprove it on all the three metrics, the metrics that you used in the first place, to get approval.

DR. KIBBE: The argument that you are making is that because the criteria says that all three of these parameters have to meet the criteria to get approval, doesn't necessarily mean that we shouldn't require all three to meet the criteria to get unapproval.

By saying okay, in the original submission, all they had to do is fail one to not get approval, that's fine, but now we have an already approved product, and we are doing a test to show that it is not equivalent, so I would like

to see it demonstrated that it is not equivalent on the same three parameters, and if it can't do it on all three, then, it has failed that test, just like it would have failed originally to get approval by failing one of the three, and that is my argument.

DR. SINGPURWALLA: Off the record. To really look into this issue, it is a much more serious issue that what meets the eye. There is a rule that has been set up, and you have to live with that rule, I agree with you, but what is to stop the FDA from looking to the future and changing the rules?

DR. HUSSAIN: I think that point is well taken, and, Helen, actually that is exactly what my new instructions were from her, so we will take this further into discussion, and so forth.

I think this was very valuable, and I am not fully sure exactly that we have come to a conclusion on this yet.

DR. KIBBE: Jurgen and I have come to a conclusion. Marvin's conclusion is slightly variant, but not too much.

DR. MEYER: But I am retiring.

DR. YU: I guess that we are back to the April 14th situation where there is 1 versus 3.

DR. HUSSAIN: Lawrence, I think it is time to stop the discussion.

DR. KIBBE: I think the Agency has to step up to the plate. We have given you the best advice we can.

DR. YU: Okay. Thank you.

DR. KIBBE: I think it is appropriate at this stage, since my schedule says we are taking a break, to take a break.

We are breaking 15 minutes early. We will give you 10 minutes. We expect you back in your seat at three minutes to 3:00, and at 3 o'clock, we will have our discussion about the locally acting gastrointestinal materials, and we will wrap that up in short order because Gordon has the exact answer we need right here.

[Recess.]

DR. KIBBE: Ladies and gentlemen, the clock on the wall says it is three minutes to 3:00,

and as it is my tradition, I will remind you to gather and begin.

We have one more topic area.

Lawrence, are you going to set the topic up? You have got three minutes.

DR. YU: Yes, I will. Actually, I can finish within two minutes.

Bioequivalence Testing for Locally Acting Gastrointestinal Drugs

Topic Introduction

DR. YU: The bioequivalence testing for locally acting drugs was I think presented to you, and I saw the comments. Well, today, we are going to discuss the real issue of bioequivalence testing for locally acting drugs. I will introduce this topic, and Gordon from the University of Michigan will give the talk on Scientific Principles, and Robert Lionberger from the Office of Generic Drugs will give you specific examples.

Again, bioequivalence is defined as the absence in the rate and the extent of drug absorption.

As I said yesterday, the pharmacokinetic measure for bioequivalence method for systematic drugs is well understood, well used. We have pulled many, many products.

The issue remains for locally acting gastro and GI drugs. The part of reason for that, because the plasma concentrations may not be relevant to locally delivery bioequivalence, for example, a topical, nasal, inhalation, which I presented to you yesterday.

The point we want to make sure that the dissolution controls the delivery to the site of action, whether it's the jejunum, jejunal ileum, or colon. The drug concentrations in plasma are downstream from the site of action, unlike for systematic drugs, the drug ending systematic first, then, get the side effects action, for example, heart and liver, and so on, the heart and the brain.

For GI acting drugs, there is no alternate absorption path because already they have to be absorbed from the gastrointestinal tract. So,

bioequivalence approach the Agency has used, for example, the clinical study of vancomycin, pharmacokinetics study is sulfasalazine, the in vitro study is cholestrylamine.

What we want is want to develop a scientific basis for the choice of BE method, bioequivalence method, which we need your input on role of pharmacokinetic studies, role for in vitro dissolution studies, role of the clinical studies.

With that short introduction, Mr. Chairman, I finished it within two minutes, I turn the podium to Gordie.

DR. KIBBE: Thank you, Lawrence.

Dr. Amidon.

Scientific Principles

DR. AMIDON: Thank you. I am glad we are recovered from that discussion of statistics. I know I get glassy-eyed. I think Qian Li did a great job, and then we turned it into chaos, but that is our job, I guess.

MR. CLARK: Chaos theory is our goal.

DR. AMIDON: What you received in the

handout was the unedited version of my presentation, because it was done before I knew what Lawrence and what Rob were doing, so I am going to skip a lot of the slides that I have because points are already being made, and talk about the highlights, the essentials of my point, and I will give you the executive summary right now.

First, bioequivalence is the question of dissolution. What else is it? The same drug in different products. Once the drug is absorbed, it is the same except in the unlikely scenario, there is maybe a competitive metabolism inhibitor or an excipient that might alter permeability. Evidence for that is limited in vivo in humans.

So, bioequivalence is a question of dissolution. That is where the science needs to be done. So, the bottom line for GI drugs, for all drugs, is that we should put more emphasis on the science of dissolution and what I think of as a bioequivalence dissolution test. So, that is going to be my bottom line, big picture conclusion.

The subconclusion for GI drugs is that I think what we need is a bioequivalence dissolution test with some type of in vivo test, perhaps not a confidence interval test, maybe a point estimate and an interval requirement, say, between 90 and 110, so that we don't have this confidence interval issue.

You could argue do we need the in vivo test. I think in some cases, we do not, and probably we need to go drug by drug for locally acting drugs, and Rob will talk about specific drug examples.

One of the issues in setting up a policy issue is try to be very general, and you get into trouble because some things aren't generalizable very easily. So, I think we will have to regulate GI drugs, of which there may be a half a dozen that are very important, more on a drug-by-drug basis, or maybe classify them, I don't know.

So, that is the bottom line. Dissolution is what we should be looking at, and a dissolution test plus an in vivo test, perhaps a point estimate

would be enough.

I am going to skip over most of these slides, because the points are already being made.

The one point that I will make, that I make all the time, and I think is generally accepted, at least no one has argued, is that I think bioequivalence is maybe the single most important regulatory standard for virtually all products on the market today.

That is, products on the market today, are on the market because of either proven or assumed bioequivalence. If not, what could we say about the clinical? We have to make that connection, the connection between the product in the bottle and the label is bioequivalence.

Yes, of course, we have to have the potency, the impurities, and we have to have the standards, but bioequivalence, so this is I think one of the most important issues in drug regulatory standards in the world today, because it pertains to all products. My interest, of course, is in oral products.

There is some caveat in the Orange Book, just to point out kind of the legal basis. If you look at where I think the most up-to-date definition of bioavailability and bioequivalence, it is in the preface to the Orange Book.

It has been revised periodically over the years, I think no one has noticed it, because they slip kind of changes into the Orange Book, it just comes out, and life goes on. Right? Is that what you do?

At any rate, for locally acting drugs, it says, "Where the above methods are not applicable, e.g., for drug products that are not intended to be absorbed into the bloodstream, other in vivo or in vitro test methods to demonstrate bioequivalence may be appropriate."

That is where we are at here with GI locally acting drugs.

Again, I am going to skip through these. You have seen this. Rob is going to use this, so I am going to skip it, the disconnect for locally acting drugs.

Now, classically, we do Cmax, AUC, of course, and AUCt, and we have confidence interval test, but if the levels in blood are very low, we have a problem, so we have a practical problem.

So, I am going to come back to the paradigm for bioequivalence. I think of the paradigm of bioequivalence today as being the following, starting at the top. Similar plasma levels, similar pharmacodynamics, similar efficacy to the label. I mean that is the implication, similar pharmacodynamics.

Then, similar in vivo dissolution, similar plasma levels. For oral products, I think maybe for all products, but certainly for oral products, similar in vivo dissolution. When we think about the physiology of oral absorption, the drug dissolves and is spread along the gastrointestinal tract and absorbed. We think of absorption as into the intestinal mucosal cell.

Subsequently, systemic availability is later, and there is more stuff, drug stuff, you know, liver in between. That is part of the

complication, we are doing bioequivalence based on plasma levels, which is systemic availability. We are doing a systemic availability test which is distant for GI drugs from the site of action.

So, similar in vivo dissolution, similar plasma levels. So, then, where the science is today is in vitro dissolution. We need to be more rigorous in how we do dissolution when we use it for bioequivalence materials.

We think that there is no reason why we cannot establish better dissolution methodologies that reflect the in vivo dissolution process. I think that would have a number of implications including accelerating the drug development process, because when you are making a product and then testing it in humans, you would like to have a good idea you are going to succeed.

In order to do that, you have to have a dissolution test that reflects what is going on in vivo. So, I think better dissolution can be a big step in advancing and accelerating drug development.

So, that means doing something. Often now today, we have what we call biorelevant dissolution media or biorelevant dissolution. I think we need to use that term carefully because, you know, to take some natural surfactants and a little bit of phospholipid and put it in water and shake, you either have a drug delivery company or you call it biorelevant dissolution media, but what is it? There is no evidence that it is relevant to the in vivo dissolution process.

So, we need to establish that connection between the in vitro dissolution methodology and the in vivo dissolution process, and I think that is where there is a big gap in our knowledge today, not just for GI drugs, for all drugs.

So, my point here is broader than just GI drugs, but similarly, if we had confidence in an in vitro dissolution test, that is all we need to do. That is all we need to do. So, we should be focusing the science on that dissolution test.

I am preaching too much here, so I am going to skip most of my slides, but I have to show

at least an equation. I noticed that on my badge, they had MA. It took me a while to remember that I had a Masters in mathematics, and I was impressed.

The FDA is so thorough in their investigation of my background, you know, every year I have to fill out all these conflict of interest things. They actually put MA. That is the first time that has ever happened, so I have to compliment the FDA and their thoroughness in investigating my background. But I did pass, and I am here.

Anyway, this is the equation of bioequivalence, but I am not going to talk about it.

We talk more about the physiology of gastrointestinal tract and product disintegration, dissolution, and spreading along the gastrointestinal tract. That is where the investigation is. That is where we need to do more investigation.

Again, I am skipping most of the slides.

So, to kind of come to the conclusion on

the bioequivalence for locally acting drugs. I mean obviously, plasma level is downstream from the site of clinical effect, which is local. The local site of action is in the GI tract.

So, dissolution and transit in vivo controls the presentation of drug to the site of action. So, this is where plasma levels are probably less good than a good dissolution test.

Now, we could, with intubation, measure concentrations along at least part of the gastrointestinal tract, not easy to do, and, yes, you have got tubes in, so it is not normal. You could argue is that feasible.

Now, I think most locally GI drugs are low permeability, but I now would want to caveat that, I am not sure that is the case. There is certainly low systemic availability in general, and that is probably more the issue, because that makes the in vivo test plasma levels more difficult to measure.

So, for locally acting drugs, in vivo dissolution is the key determinant. So, for the in vitro dissolution test, we should cover the range

of in vivo variables.

So, here is the hypothesis. If a product dissolves, two products could be the same manufacturer, but they just did some reformulation. If those two products dissolve at the same rate under all in vivo conditions, such as pH, 6.5, 7, 7.5, maybe a couple more if you want to be really rigorous.

That means that the two products will perform the same regardless of what the pH profile is in an individual subject. That is what we have to ensure, and I think we can do that better with an in vitro test than an in vivo test.

Now, might want to debate do we want to do 6.5, 6.75, you know, but we need to first accept in principle that a dissolution test is a key crucial, I would say an essential component of setting a bioequivalence criteria for a GI drug, because I think that is the case.

Now, one place we could start is that biowaivers for Class I drug, if a GI drug is a Class I drug, high solubility, high permeability,

and rapidly dissolving, it is all over, it doesn't matter.

In this case, the GI drug would be low permeability or certainly low systemic availability, it may or may not be low permeability. So, I think that is the equivalent to extending biowaivers to Class III drugs--I am sorry--that is Class I drugs.

What we are talking about for low solubility drugs or particularly low permeability drugs would be extending biowaivers to Class III drugs, which has been proposed. I don't know if there is any examples, and maybe Rob will talk more about that.

I think for pH, we want to look at dissolution as a function of pH. The one product that I am going to show just some data on, I think Rob is going to show the same data, so I will be quick, is mesalamine. It is in enteric coated dosage form.

The question would be do we need surfactants or not, and that would depend on the

drug, because if the drug is poorly soluble, then, we get into the spiro-relevant [ph] dissolution media, and that is a bigger question.

So, I think we should require a dissolution test for bioequivalence in the bioequivalence criteria for acceptance criteria for GI drugs, that we need to consider the pH and time that the drug will spend in the stomach and in the gastrointestinal tract. I can propose those if you want to discuss them.

I think what is more important is accepting or at least advising and recommending to the FDA that in vitro dissolution testing should be part of considering the bioequivalence requirement or testing for a local GI drug.

You would have to use the similarity, you know, the 10 percent difference or F2 comparison for dissolution profiles.

The dissolution test actually is a difficult criteria, I think. Mesalamine, I will show just a few slides on that, but mesalamine is an enteric-coated, local acting drug, and are some

dissolution profiles done by Jennifer Dressman, now at Frankfort, published in European Journal of Pharmaceutics and Biopharmaceutics, but here are different products and simulated gastric fluid.

Here is a pH 6.8. You see, none of the products would be similar. They all dissolve at a different rate, and that is a surprise to development scientists, and these are different products. I don't know if they were approved as bioequivalent or not actually, but I do not think they would be bioequivalent in the gastrointestinal tract even if they were bioequivalent in vivo.

There are some other profiles again showing that they are quite different. If you increase the pH to 7.8, more of them become similar because they all dissolve rapidly above the pH of the enteric coating. So, if you do a dissolution at a high enough pH, you can make things look mostly similar, but at the critical pH where dissolution is occurring, they would be different.

So, I think that the pH dissolution profile requiring similar dissolution at, let's

say, in this case we are looking at I think like a pH of 6.57, 7.0, 7.5, that pH range. We can debate whether you should do pH 6.0 would be critical.

I am going to skip these because these questions are already up.

So, what I want to propose that the committee consider and perhaps recommend to the FDA, I am not sure, I guess we are going to go through a list of questions that Rob is going to discuss, but that we do require in vitro dissolution as part of our bioequivalence testing for drugs that are locally acting, and that then the in vivo test, do we need an in vivo test for safety purposes, for safety assurance purposes, and do we need a confidence interval test for in vivo.

I think that may be on a drug-by-drug basis. You may not want to try and make a decision for all locally GI drugs. I think depends on the pharmacology and metabolism of the drug.

But I can say that if had a rigorous enough in vitro dissolution test, in vivo testing would not be required.

That's it. Thank you.

Do you want to have questions now?

DR. KIBBE: Shall we do that, because I think Marvin has a question and so do I. Go ahead.

DR. MEYER: Real quick, Gordie.

Do you think that F2 is an adequate parameter to use in making a bioequivalence decision?

DR. AMIDON: The answer is I don't know, Marvin. I have suggested this to a couple of people, that we need to evaluate that, and whether F2 or 50, where did that come from, and is it enough, and the answer is I don't know.

I think that the statistics of dissolution and the dissolution variability that you could allow, that would keep you within the bioequivalence 80 to 125. Now, that is not so easy to answer, and it is going to depend on drug properties, but I agree, that the F2 or 50 needs more investigation.

DR. KIBBE: Anybody else? Go ahead, Judy.

DR. BOEHLERT: I finally have a question.

By making this suggestion that the in vitro dissolution is a factor, does that presuppose that the clinical efficacy of this drug only occurs in a very narrow pH range, so that this pH difference you see on dissolution is meaningful, because they could be clinically equivalent or have the same action, and have different profiles at different ph's because where the drug acts is across the GI tract, and not just one location.

DR. AMIDON: They could be clinically equivalent with a different dissolution profile, but you would have to prove it to me. No one is going to do that.

DR. BOEHLERT: And how would you do that?

DR. AMIDON: But my answer, I think more to the point, I think, Judy, is the pH profile changes through the GI tract, stomach, duodenum, jejunum, goes 5.5, 6.0, 6.5, and it varies from subject to subject, and in a fasted/fed state, during the different Phase I, II, III, of the fasted/ state.

So, what you want to do is ensure the two

products will dissolve under any of the pH conditions that we would see. So, if they dissolve the same, let's say at pH 6.5, 7.0, 7.5, you could say, well, maybe we should 6.0, maybe 5.5, maybe we should pretreat for 15 minutes in 10th normal HCL for a while, pretreat for 2 hours, maybe we should pretreat at pH 4.0, because that is more like the average pH in the stomach with food.

So, I think that is more of an issue of the specific test, and that is going to be a more elaborate test than our typical so-called dissolution test.

DR. BOEHLERT: Actually, I guess my only concern was if, indeed, the drugs were equivalent at pH 7.8 where it all dissolved at the same rate, is it really meaningful that it was different at lower pH's.

DR. AMIDON: I would argue that it is, because the pH in the intestine in humans is more like around 6.5 to 7.0, and it goes down to 5.0 or 5.5 in the duodenum where you have got the mixing of gastric acid and pancreatic and bile, so that I

would say 7.8 is actually not relevant.

I wouldn't do that. The highest I would go would be about 7.5.

DR. KIBBE: Paul.

DR. FACKLER: If I can just make a couple of points. First, I agree about the dissolution and how inappropriate the dissolution we do today is to certainly the way orally absorbed drugs are taken. I can't remember the last time I saw somebody drink 900 milliliters of water with their tablets.

DR. AMIDON: Or even 250 ml.

DR. FACKLER: Or even the 240 or 250 that we use in the clinics. But let me ask a question. For systemic drugs, we look at the plasma concentrations of the compartment just prior to the site of effect, and for these drugs, we might look at the plasma compartment as adjacent to the site of effect just after it, and so in either case, it might be a good surrogate measurement for the amount of drug at the site of action in our traditional case where we have been doing it for 20

years, it is just prior to, but for these drugs, we might consider it just post, and maybe as a surrogate marker for the amount of drug that was at the site of action.

DR. AMIDON: I would say the following. I think that is a good question, Paul, and I thought some about that. Two things I would say. One is the drug as it spread along the gastrointestinal tract, depending on how it is released may be absorbed in different segments, so the drug might actually be presented to different sites from different formulations, and still meet a Cmax and AUC criteria.

Now, if you were to add in Tmax and/or some absorption rate measurement in comparison, then, I would agree with you, it would be equivalent, but that is complicated. I mean the FDA has looked into measures of absorption rate other than Cmax and concluded that there isn't really any good measurement.

So, the answer is if you measured rate and Tmax and had criteria on that, I would say then

plasma would be just the same basically, but if the drug is very highly metabolized, so the systemic availability is low, and you are measuring parent, and assuming there is no problems with metabolite, which you can't assume, then, you have got the variability issues on the plasma site, so the plasma site could be a much harder test.

DR. KIBBE: Jurgen.

DR. VENITZ: I think in general I buy the idea that in vitro dissolution could predict in vivo dissolution of those products, but you mentioned kind of in passing excipient effects on permeability or metabolism. What about food effects? In other words, food constituents would considerably at least have the same effects on either permeability and/or metabolism, which may affect locally what is going on.

DR. AMIDON: For bioavailability, I would agree, Jurgen, it would have a big effect obviously, but for bioequivalence, I would say the effects would tend to be washed out by the dilution of the food of any excipient effect.

So, I think when we are comparing two products, the same drug, I would say it is a less important issue.

DR. KIBBE: Anybody have something because I have got a whole bunch?

DR. MORRIS: I have just one quick one. Gordon, were you assuming that this would be done in the normal dissolution apparatus or is that an open question?

DR. AMIDON: That is an open question in my mind, yes.

DR. MORRIS: Because I think there is a fair amount of concern, hydrodynamic at the very least, with the current apparati. I just wondered if you are not restricting it to that.

DR. AMIDON: I guess my position is changing dissolution apparatus should be done with great care and with good justification.

DR. MORRIS: Oh, absolutely.

DR. AMIDON: But I believe that a bioequivalence methodology needs to look at reflecting in vivo processes, and we should start

with that.

DR. MORRIS: I agree with your premise.

DR. KIBBE: I follow up on Ken and go down a road with a lot of variables in it. I love in vitro tests if I have control of all the variables, and when I start losing control of the variables, then, I start to get worried about the test.

I can imagine two products that have slightly different excipient compositions who appear, in a dissolution apparatus, to dissolve equivalently, but that they aren't presenting the same amount of drug to the surface of the membrane for one reason or another.

There might be an excipient in there that forms cells that trap some of the drug, there might be an excipient that binds the drug, but in a dissolution apparatus, the excipient is small enough so that it goes into solution, but then it doesn't allow it to release.

I can imagine interactions between food substances that are different for this dosage form versus that dosage form. I mean I really would

like to go back to the if you could show me that both formulations have the same inert or inactive or excipient ingredients and in the same basic dosage form, then, I am really happy with dissolution studies as a mimicker because we are really looking at the levels of drug in that lumen, that then gets presented to the surface where it is supposed to have its effect.

The other thing that I wonder about is if some of these excipients are permeation enhancers, than one drug, they both would dissolve the same in the in vitro dissolution apparatus, but the one with the permeation enhancer would start to leave the site where you want it and end up in the blood supply where you don't want it, and you really have to link that to some marker at the back end to see how fast it is leaving where I want it to be.

If one gets into the body in this case better, that's worse.

DR. AMIDON: It could be, at least in the systemic circulation.

DR. KIBBE: So, the questions that I come

back to is what is the dissolution apparatus, what are the criteria that we have to put on the product to narrow it down, so that we know that the dissolution apparatus can tell us if the two are behaving the same before we put it in a person, and then when we do that, aren't we better off still getting minimalist levels in the plasma just to look for the odd chance that one of them is permeating better than the other, so that we can either prevent levels going up, so that we might have toxicity in one or the other, or prevent levels being too low, so that we have some secondary measure.

Now, if we are going to do that, which one does a better job of actually measuring the drug at what I would call the biophase where the drug is having its real action, and I really think they both measure it incompletely.

DR. AMIDON: One side and the other. We have got it sandwiched in between, right?

DR. KIBBE: Right. So, I would argue that you have to do both somehow.

DR. AMIDON: Maybe we need an intermediate step here to get more experience. So, I could see where we might require some type of pharmacokinetic measure, plasma levels, as well as dissolution, both. That is, I am recommending both.

Now, I believe that when we know enough, and maybe for some, maybe most, but probably not all drug products, dissolution would be enough, but we are not there yet.

DR. KIBBE: I could support that once I start narrowing down my variables.

DR. AMIDON: So, we get into the discussions of dissolution, but I mean and I could throw things out, but it is going to take more than me to kind of evaluate what might be a good criteria here and dissolution methodology. I think what is important at this stage for the committee is to say, yes, we think this is the right path to go down and tell the FDA to figure it out, like Congress does, you know, you go figure out what to do with bioavailability.

DR. KIBBE: Ken wants to say something

else.

DR. MORRIS: I have two caveats I guess, the first of which is that in that dissolution is a manifestation of the product itself, as we have discussed, I like that because it is looking at changes in the product.

But aside from the apparatus issues and the tactical issues, there is the statistical sampling issue that we still face with our normal dissolution testing that I think is probably only addressed by the consistency that we had hope to achieve.

DR. AMIDON: Statistics will be here, too.

DR. MORRIS: Yes, sir. I was going to insult Nozer, but he has left already.

DR. KIBBE: Marvin.

DR. MEYER: Gordie, what do you with the situation where your in vitro is too discriminating? You have three different products and clinically they all work, maybe to different degrees, but close enough, and yet your dissolution says there is a 20, 30 percent difference.

DR. AMIDON: Good question, Marvin. I have tried when I talk about dissolution and talk to the dissolution people at the FDA, say do not use the word discriminating, because that is not what your job is. Your job is to ensure in vivo bioavailability.

If the manufacturer wants to be discriminating because of his quality standards, that is fine, the manufacturer can do what he wants as long as he meets the standards that ensure bioequivalence.

So, I don't think the FDA should be regulating on the basis of discriminating dissolution tests. I think they should be regulating on the basis of a test that will ensure in vivo bioequivalence. I don't know if anyone agrees with me, maybe you do, but I don't like the term discriminating because you can always get discrimination.

DR. KIBBE: Ajaz wants to say something.

DR. HUSSAIN: Gordon, I think you put something right on, and that is a challenge. The

last several months we have been struggling with this in a sense. I did share with you my presentation to the USP meeting, and so forth. Since we do not have a good handle on variability because of the calibration issues, and so forth, I think the tendency has been at the Agency to say, all right, how do you minimize that.

I want a big difference, so I feel confidence, and I think the time has changed to say what is the intended use, and so forth, so I think the point you made, I don't think we have consensus throughout right now, but it is a very important point, and I think we have to move in that direction and sort of discuss and debate that.

DR. KOCH: I just had a quick question that goes back to some involvement I had maybe over 20 years ago where there was a dog model set up, and I imagine it could be most animals where they actually had a trapdoor on his stomach, where you were able to, in this case, primarily watch disintegration and subsequent effects by monitoring plasma levels on dissolution.

But is there any development that could be called pseudo in vivo to check for absorption, not to do what we are talking about here, but sometimes there is a question somewhere between the in vitro and the in vivo?

DR. AMIDON: I think my answer to that question is no, there is no way to make a step forward dosage forms. I would say we regularly test in dogs, recognizing, though, that the average pH in the upper small intestine of dogs is about 1 pH unit higher than humans, so therefore, enteric-coated products are not going to be reflected by the dog.

We do controlled release in the dog, but we only look at the first 6, 8 hours at most, because of the shorter transit time, and you have got to just discard any data after that.

The dog, as I understand, is not basogastric acid secreter, so the pH in the stomach is much more variable. So, the answer is I don't think it will do the job for this, and any smaller animal you can't do because you can't scale the

dosage form down very well, or can't at all maybe, I guess. I mean make an enteric-coated tablet for the rat and scale it up to humans, you have got bioequivalence issues again.

DR. KIBBE: The pig is really good. Meryl?

DR. KAROL: Am I assuming correctly that the question really is are we going to test for bioequivalence locally, that includes the pulmonary tract, as well as the GI tract?

DR. AMIDON: Me, no, I am not ready to go that step in terms of topical or inhalation although I could make some case that the principles apply. The difficulty with topical, for example, is that you are putting your formulation in direct contact with the absorbing surface, so the formulation will affect, let's say, the permeability of the skin.

The big saving grace about the gastrointestinal tract is there is this big dilution in the stomach, and that is why I think the excipient effects are small. I mean we have

got this big dilution in the stomach, so all the excipient effects are diluted out.

DR. KIBBE: We can talk about that.

DR. AMIDON: Inhalation, also, there is the physics of the dosage form particle size and deposition along the GI tract, so I am not an expert at that, so I am not very knowledgeable about that. This is focused on GI.

DR. KIBBE: Ajaz.

DR. HUSSAIN: I think the other aspect is if you recall the discussion Rob Lionberger had presented on topical skin products, there is a fundamental principle that is evolving, it is quality by design.

What that means is in a sense, comparing formulations at anything worth critical and then trying to relate that to that, and I think the aspects of excipient similarity, and so forth, a lot of this formulation information can be supportive information that can give you all this, and so forth.

So, I don't want to discount that in the

sense I think Rob Lionberger's presentation on the topical decision tree had those elements, so in many ways, I think the proposal for looking at an in vivo relevant bioequivalence test using in vitro method is a confirmation of all that similarity or all the design that sort of comes through.

So, keep that in mind as you think about it.

DR. KIBBE: Ajaz, that was clearly the point we get to. Once we get an understanding of the formulation itself, and can look critically at what is in there besides the active, then, we are much more confident in what Gordon is proposing as a way of measuring what is happening because if we know there is nothing in there that has a habit of doing the things that might disrupt it, then, we are done.

I still think that we are going to find early on it is going to be very comforting, if you will, to get some blood levels just to make sure that there is something that we haven't expected that is happening, but I think we need to go in the

direction of dissolution testing. I think that is a wonderful way to go in a situation.

Anybody else?

We have another presentation, right?

DR. AMIDON: Right. Thank you.

DR. KIBBE: Thank you.

Dr. Lionberger.

Regulatory Implications and Case Studies

DR. LIONBERGER: What I am going to talk about is just give some examples that are illustrates of how we apply some of these scientific principles to several different products with the intention of sort of spurring discussion although we have already had some very good discussion.

The first scientific issue is dissolution, we are not really going to talk about because you have had a very good discussion about dissolution.

The second scientific issue that I want you to keep in mind through my presentation is the issue of sort of how we should interpret pharmacokinetic measurements that we make on the GI

acting drugs.

Certainly, they are related to safety, but I also want to just indicate that, you know, you often hear that the peak pharmacokinetics of locally acting drugs aren't correlated with therapeutic effect, so I want to sort of focus your attention on the sort of last point here, on how the pharmacokinetics of the GI acting drug is related to formulation performance, and that will sort of lead into some of the discussion that we would like to have on how we should use pharmacokinetic data in evaluating bioequivalence.

So, the first example that I want to talk about today is for the drug mesalamine. This is an anti-inflammatory drug mainly targeting the colon. It turns out that it is actually pretty rapidly absorbed from the intestine and this drug can be measured in the plasma. There is also some extensive metabolism pre-systemic circulation, as well.

The one thing that is sort of interesting about this drug is sort of a case study, is that

there is a wide variety of formulations of this drug that are currently on the market, so you can do a lot of sort of comparisons to see which different types of tests can actually distinguish between these different formulations.

The sort of key scientific issue that is driving these formulations is you want the drug to target basically the colon, but it is rapidly absorbed, so the formulation technology is either pro-drugs or some sort of delayed release enteric coating are designed to sort of keep the drug from being absorbed until it reaches the target.

So, this sort of raises the issue of targeting different areas of the gastrointestinal tract and some of the issues that that might raise.

The first product is sulfasalazine. This is the oldest mesalamine product. It is the third molecule down in the chemical structures, and it is a pro-drug that consists of mesalamine moiety and then the other moiety, sulfapyridine.

For this case, the mesalamine acts locally. The other moiety of the product is

actually rapidly and quickly absorbed. So, this drug is old enough that OGD has actually approved ANDAs for this product, and the basis for the bioequivalence determination in this case was pharmacokinetics, but it was the pharmacokinetics of the inactive part of the pro-drug, primarily because it's rapidly absorbed and it has much lower variability than the active moiety itself.

Also, for this drug, the sulfapyridine itself has pharmacological activity, and there are also its systemic exposures is highly related to some of the safety issues with this product.

So, for this product, this moiety was used primarily because, as we will see later, there is a high variability associated with the pharmacokinetics of the active ingredient itself.

So, that is sort of just one example, and Lawrence sort of pointed these out, that sort of in the past, FDA, for these GI acting drugs, has used sort of a wide variety of different ways to evaluate bioequivalence, and we would like to sort of put together a sort of more fundamental

scientific framework on sort of when we should use which aspect.

So, a second mesalamine is the Pentasa product, and this is a slow release, microgranular formulation, sort of releases continuously through the intestine. It is not really pH dependent on how it releases.

During some of the development of the evaluation of the NDA for this product, there are PK studies attempted for bioequivalence between pilot and production scale products. Again, here the issue was we weren't really able to conclude bioequivalence because of the high variability of the active ingredient, but they were able to establish in vitro/in vivo correlation between dissolution and the pharmacokinetic studies, and that was used to demonstrate equivalence between different pilot and production scale formulations for that particular product.

So, a third mesalamine formulation is the Asacol product. This is a delayed release, coated formulation, and here, there is pH sensitive

dissolution that allows it to target the colon.

So, when you have all of these different products, we can look at sort of the different possible ways of testing these products. The discussion points that were presented to the committee were what is the role of dissolution, pharmacokinetics, clinical studies, so that we can look at these types of comparative studies between these different formulations to sort of get at least some sort of solid basis for discussion.

Gordie in detail showed this data on the dissolution studies of mesalamine products, basically different a pH-independent product. These are mainly European formulations, they are not the formulations that are marketed in the U.S.

You can definitely see that at the low pH, you see only the sort of slow release product dissolving. As you raise the pH, the different enterically-coated products start to dissolve depending on what pH they are particularly targeting.

So, by choosing appropriate dissolution

conditions that are relevant to the in vivo conditions where the product started, and you can distinguish between the different products and what region of the intestine they may be targeting.

There is also some studies that have done comparative pharmacokinetic studies. Again, here is sort of a pellet and tablet type formulation, not the sort of currently marketed formulations, but sort of similar ones.

You see in this case, you look at the Cmax and AUC. Definitely, in this case, the pharmacokinetic studies actually show a large difference between the products, but again, here, this is just scientific publications for these. It is small sample sizes, so they didn't evaluate confidence intervals, but the variability of the measures for these drugs are very high.

So, that sort of complicates the determination of bioequivalence using pharmacokinetic measures.

So, with all these different products on the market, there has been some interest in trying

to say which one clinically is more effective. So, there have been, not complete head-to-head trials between all products, but there have been a large number of clinical studies, and sort of a recent review, came to the conclusion that clinical studies haven't been able to demonstrate significant differences in the efficacy between existing mesalamine formulations and stuff, two examples here, but there are sort of many studies available in the literature.

So, if you were trying to sort of determine equivalence between two formulations, you might have a very hard time using the clinical study to have a sensitive discrimination of formulation performance, because these existing formulations, which use very different technologies, aren't very well distinguished by sort of clinical studies using the usual efficacy endpoints.

So, if we just summarize the mesalamine example, if we want to sort of distinguish the current products, we would probably yes, if we

chose the right dissolution criteria, we could clearly see the difference between the products.

Pharmacokinetics, it looks like again we could see the difference especially because if the products release early, they are rapidly absorbed. If they are delayed into the colon, then, the absorption is much slower, so differences in local release actually do show up in the pharmacokinetics through especially Cmax for this case.

But again, with this particular product, there is the issue of pharmacokinetics of highly variables. If you want to do clinical comparisons in terms of the bioequivalence study, again, that would be very challenging in terms of getting a sensitive test of the formulation differences.

So, just to bring in a slightly different example, another example of a locally acting product is Acarbose. This is an intestinal enzyme inhibitor that acts to reduce glucose absorption. For this product, there is no measurable absorption, so you can't use pharmacokinetic studies, however, there are pharmacodynamic

endpoints available.

Again, you can look at changes in glucose or insulin level in response to a meal with the use of this drug or a comparator product.

Here, one sort of interesting thing to think about is when we think about the pharmacokinetic studies, like the pharmacodynamic endpoints, are usually downstream measures of the formulation performance, in the same way that the pharmacokinetic measurements are here. So, there is some sort of mathematical similarity between how we might interpret pharmacodynamic endpoints and pharmacokinetic measurements for GI acting products.

Another example of a product where there is not much detectable absorption is cholestyramine. This is a bile acid sequestrant, essentially binds to cholesterol in the intestine.

This is sort of an older product. In 1993, FDA guidance recommended using an in vitro binding assay to demonstrate equivalence of these products, so there is no dissolution of

pharmacokinetics. These assays measured affinity and capacity.

One of the issues, here, we talked a little about the role of excipients. For these types of products that are involved in binding there, then, you sort of worry that if there is differences in the excipients in the formulation, that that might make a difference in how they bind to other products, and these types of in vitro binding assays can be valuable and interesting, those types of concerns if they are relevant to a particular product.

So, before I lead into our discussion, I just want to sort of return again to some of the scientific issues that were raised by the GI acting drugs.

The first is the BCS classifications and biowaivers again for systemic drugs. If we have high permeability and high solubility drugs in rapidly dissolving dosage forms, we often consider waiving in vivo bioequivalence studies.

So, the question is how should we extend

this to GI acting drugs. I think one more question is what should the permeability play. If permeability doesn't play any role in the absorption process, should we extend the biowaivers to sort of all highly soluble drugs in rapidly dissolving forms irrespective of what their permeability is, or is there something about the classification of drugs in terms of high permeability, low permeability that may make that more risky, perhaps interactions with excipients or the role of absorption in the intestinal tract.

So, that is one of the issues that we might like to have some discussion on.

Again, I just want to come back to the issue of the role of pharmacokinetic studies in the absorption from the GI tract. Again, for a systemic drug, what you see is that the formulation performance is what we are really trying to make a determination about. Again, this essentially is controlled by the dissolution.

The drug goes through the absorption process, reaches the plasma concentration, and that

is the place where you take a pharmacokinetic sample, and that is also the place where the effect of the drug takes place.

So, the difference for a GI acting drug is essentially the relationship between sort of the formulation performance, pharmacokinetic sample, that is still the same, but the only thing that sort of moved is where the effect is taking place.

If you think about how we conduct bioequivalence studies, we usually conduct them in healthy people. We don't really concern ourselves with the effect, so that whatever connection we are making for systemic drugs between PK sampling and formulation performance, the connection is still there for the GI acting drugs.

So, I think the big concern with looking at the pharmacokinetic studies in the GI acting drugs is essentially when, for the systemic drugs, since we know the effect is taking place where we are taking the sampling, we have some sort of intrinsic way to know what a significant difference is.

We sort of say 80 to 125 percent difference in the plasma concentration is sort of a general definition of clinical significance, so we know that if we meet that, that sort of gives us an idea of what equivalent formulation performance is.

When we go to the GI acting case, where the effect is now separate, we don't have that connection as to what the calibration is between difference in pharmacokinetic sampling and a significance clinical effect in the same way that we do for the systemic drugs, so that I think is the issue for interpreting the pharmacokinetic studies is we don't have the sort of intrinsic calibration of how significant the effect on formulation performance is.

But still the relationship between formulation performance and pharmacokinetics is still there in both cases in a way that maybe it is not for other locally acting drugs, say, inhalation products where you have the case where if the product reaches the lungs, it also can be absorbed by different pathways, and you are not sure that it

is passing through the exact same pathway.

For the GI acting drugs, you know that in both cases, it is being absorbed through the same site.

Just to lead into sort of the specific questions that we wanted you to discuss, just sort of outline, a sort of potential framework for thinking about bioequivalence of locally acting drugs, sort of the first point would be again the sort of critical importance of dissolution testing in conditions based on understanding of the formulation and how it interacts with the in vivo environment, so choosing the right conditions for in vivo and in vitro dissolution testing.

The second part of that is pharmacokinetic and pharmacodynamic studies. Again, the sort of potential we always see for those is really, they sort of confirm the dissolution testing. They confirm the relationship between the in vitro dissolution testing and the in vivo dissolution, which determines product behavior.

They are also important for assessing

systemic exposure in terms of any type of safety concern.

The third element of the framework is concern about excipient interactions, and if, say, the product's mechanism of action is binding to like the cholestyramine mean example, binding to something in the GI tract where an excipient could be competitive or inhibitory for that binding process, it might be useful to require some sort of in vitro assay for that type of process for particular products if there is a mechanistic reason why the excipient interaction may be important.

So, here, I just want to remind you of the discussion questions that we suggested to you.

We wanted your input on the role of pharmacokinetic studies, the role of the in vitro dissolution tests, and the role of clinical studies in these particular products.

I have sort of listed out sort of slightly more detailed versions of these questions, you know, how should we use the pharmacokinetics data,

if it's measurable, to evaluate formulation performance? What drug specific information would be valuable in sort of calibrating our interpretation of pharmacokinetic studies, when it would be valuable, when it would not be valuable?

When is it possible to use dissolution testing alone to demonstrate bioequivalence, and when do we actually need the confirmatory data from pharmacokinetic or pharmacodynamic studies, as well?

When should comparative clinical trials be conducted, what types of issues there?

The final question on who we should look at extending the BSC-based biowaivers for GI acting drugs.

With that, hopefully, we will be able to have some more discussion on some of these issues.

Committee Discussion and Recommendations

DR. KIBBE: Marvin is ready.

DR. MEYER: Kind of relating to your in vitro question, are there any drug products that are known to act locally in an undissolved state,

particles, fine particles?

DR. KIBBE: What about Sucralfate?

DR. MEYER: Yes, Sucralfate. Dissolution, PK, would that work?

DR. LIONBERGER: I think you have to consider the mechanism of action. I am thinking primarily here of drugs, you know, where the sort of mechanism of action is distinct from the formulation. I think when you have products where the sort of mechanism of action is very connected to how the drug is formulated, then, you have to have some measure of the formulation performance in vivo.

So, if you were thinking mainly of drugs where the drug is released from a formulation before it reaches the site of action, and I think there are sort of other issues where the formulation acts, just the formulation or, you know, manufacturing acts directly.

I think that issue probably will come up a lot when we look at nanotechnology.

DR. MEYER: I sort of subscribe to

Gordie's point of view. There is probably a dissolution test that will work, and I think we know enough about dissolution testing if we want to use paddle and basket and three different RPMs and five different pH's, and surfactants, and everything that anyone has ever done, and two products are equivalent under a myriad of conditions, they are probably going to be bioequivalent. "Probably" is not a good regulatory word.

DR. AMIDON: It would be very low risk of bioINequivalence.

DR. MEYER: Somebody would argue, well, that's overkill, you shouldn't have to do 89. Well, that is a lot cheaper than doing a clinical trial with these products, so that might be one approach.

DR. KIBBE: I think Paul would agree that it is cheaper than doing a clinical trial.

DR. FACKLER: Could I make a couple comments?

DR. KIBBE: Oh, please.

DR. FACKLER: Just to answer your question, there are some rectal suspensions that might fall into the category of drugs that are effective without dissolving.

My understanding of the lower part of the colon is that it is relatively water-free, and these undissolved-- mesalamine being one of them, by the way--products, hydrocortisone is another one, both of which, by the way, OGD has approved on the basis of pharmacokinetic comparability.

The other way that mesalamine, for what it is worth, is delivered to the colon is by suppository in the United States, I think. So, there is an oral tablet, there is an oral capsule, there is a rectal suspension, and a suppository, all of which are equally efficacious and making you wonder about the utility of clinical studies. I will just leave it at that.

DR. KIBBE: That is a valid point. Once you have lots of different routes of administration, and for a local effect, and the formulation effects clearly go away when you look

at the clinical impact, but remember that clinical endpoints are very wide goalposts, and we tend to, I guess being slightly anal-retentive, want narrower ones for regulatory purposes.

Just a small point. Most drugs don't act in the central blood supply, they act someplace else, and even though we measure, we measure central because we assume, having never actually verified this, assume that they are in relative strict proportionality to the amount of molecules of drug at the actual biophase, and that is the whole basis for kinetics and what Marvin and I have done for all our lives, so we are reticent to give that up, but you can't say that that is where the drug works, because that is not where it is working either.

DR. KIBBE: Ken.

DR. MORRIS: I just had a question because I think, Art, actually, you mentioned Sucralfate. What is the criteria for bioequivalence? That is not absorbed at all, right?

DR. KIBBE: Right.

DR. MORRIS: So, what is the criteria for bioequivalence for that?

DR. AMIDON: I know originally, they were doing clinical studies. There were clinical comparison studies.

DR. MORRIS: It just seemed to me I mean it would make no sense to do pharmacokinetic studies on cholestyramine, which never dissolves even when it is active.

DR. KOCH: Just to add to that, the cholestyramine is an interesting one, because from an in vitro type, you can't really duplicate the sequestering. I mean bile acid is just one of the things that it sequesters it. Basically, it's a handful of ion exchange resin, and ion exchange resins are trained to go after a lot of things where it can pick up that ion.

So, that would be a difficult one I think to just run one simple in vitro test.

Another point that I thought of when we talked about the suppository, Ajaz, when you go to Europe, do you do a check in terms of dosage forms,

as well, because it was very interesting on a European assignment, it turns out that more of our drug deliveries were suppositories than they were tablets, and someday we will start to see that as another way of administration, particularly as dosages get smaller and smaller.

DR. KIBBE: I think suppositories are much better accepted among the populace in France and Germany than they are here.

You had a comment.

DR. AMIDON: I worked with the FDA extensively and did a lot of in vitro testing on the bile acid resins, with different bile acids under differing conditions, and so it is a fairly rigorous test in terms of the capacity of the ion exchange resins to bind relevant bile salts.

I think if you look at the guidance, you would look at it and say if two resins appear the same under all of these conditions, they are likely, likely, the risk of bioINequivalence is low.

Of course, the questions in plasma, what

are you going to measure? You wanted to do cholesterol lowering. That is a long, extensive study, so clinical studies, at least I interpret here, clinical studies meaning efficacy studies are much more complicated, much more variable, and I think quite insensitive to formulation differences.

So, I think we can make an adequate case, and if you come up with something that you think might affect the in vivo performance, we can enumerate what happens in all of the components in the GI tract, and they can be tested, so we can do an in vitro test to see if it has an effect and decide whether it is relevant or not.

DR. YU: I just wanted to comment on Paul's comments for rectal suspensions, especially for the mesalamines, when we look at the pharmacokinetics, we also look at a dissolution very closely. Thank you.

DR. KIBBE: So, you have a whole body of data then on pre-existing products of varying formulation, so the Agency actually has a real good handle on whether or not there are a diversity of

excipients and could actually do dissolution testing on samples of all the products already on the market in various environments to come up with a criteria.

DR. YU: That's correct.

DR. KIBBE: Anybody else got anything? Ajaz has a comment. Good.

DR. HUSSAIN: As I think about these questions, I think Dr. Amidon and Ken Morris both have pointed out in a sense I think what is in vitro test conditions and how appropriate they are. That is a significant challenge.

I don't want to sort of jump in and say all right, BCS Class I was highly soluble, highly permeable, 900 ml, and so forth, because the volume and the hydrodynamics, and so forth, I think we have to give some thought to how we would approach that, so it is not a trivial matter.

DR. KIBBE: Go ahead, Ken.

DR. MORRIS: I guess I would just echo that. The principle I think is sound, you know, which is no surprise coming from Gordon, but the

tactical aspects of that really are quite a challenge. There is still a lot of work to do in terms of dissolution testing. As Gordon said, redesigning the dissolution test is no seed for the faint hearted, I mean that is something that is going to really take some serious scientific and engineering work.

DR. MEYER: Is it correct, Gordon, that a Class I BCS is likely to appear, at least to some extent, systemically, and a Class III similarly, maybe not so much so, but still, because of high solubility, you are likely to have something you can measure, and therefore, you could do a PK study?

DR. VENITZ: If it has high first pass effect, it might not be systemic.

DR. MEYER: That's true.

DR. KIBBE: Detectable levels are going to be a problem.

DR. AMIDON: Class III drugs tend to be not very highly metabolized, so it would probably work there, and that is where I think it is the

most important, because for a low permeability drug, there is obviously permeability dependence along the GI tract, because there is some absorption, and then it stops. It has to because it is not fully absorbed. So, I think Class III drugs is where it is more critical.

DR. MEYER: Therefore, you wouldn't need to give a waiver, you could do PK.

DR. AMIDON: You could. I am not saying you can't do PK. In fact, PK plasma levels in general, even for GI drugs, I mean if you can measure something, you know, it would give you the highest assurance. The question is what is the best test, and broadly, for bioequivalence, Cmax, AUC is our gold standard. I think our focus on Cmax, AUC has kind of preempted us from thinking about what is the real issues here, which are for oral absorption and/or, for GI, the GI locally acting drugs, the dissolution process is where the action is at, and when we want to set standards, some drugs are going to be simple and some drugs are going to be complicated, so let's try and

decide where we can simplify the standard and make it maker, and then where it is complicated, well, that is where science is today.

DR. KIBBE: I agree with Gordon. I think if you have a lot of background data, we can safely go to a dissolution test with something like this. In the absence of it, it is always nice to have a little bit of PK data, blood level data, maybe a simplified study just to get a sense for the levels, because we want to be careful of toxicity and equivalence, and it is going to be case by case.

Anybody else? Jurgen.

DR. VENITZ: I was just going to speak and for being a former clinician, in favor of clinical studies. I mean everybody here is mentioning a true statement. They are not very sensitive to formulation effects, but on the other hand, they are the ultimate relevant test. I mean they make what we are doing clinically relevant.

So, as much as I am personally in favor and moving along with looking at dissolution

testing as the base of your surrogate of in vivo bioequivalence, there is a price to be paid, and that is, we are going to find differences in those dissolution tests between formulations that clinically are irrelevant.

So, we are looking for discriminating tests--excuse the term--that discriminates between formulation differences that are clinically probably meaningless.

DR. KIBBE: And the question I guess boils down to an economic one, do I want to spend the money to do a clinical test to show obviously that the differences are meaningless, or can I do a fairly well designed dissolution test which doesn't cost me much and is very discriminating, and if I pass that, I am guaranteed that I will be okay on the clinic, and that is really what these tests are. These are surrogates for the ultimate use of the drug in 400,000 people.

DR. VENITZ: We had a similar discussion a couple of years ago when we talked about intranasal products, and I guess this committee voted in

favor, and the FDA ultimately accepted the fact that the only way to assess bioequivalence of intranasal products is the walk in the park, in other words, a clinical test.

Given the fact from my perspective that I think we understand much more about GI dissolution, GI absorption, all of which you presented, Gordon, I am personally comfortable in moving along with that, and not making the clinical gold standard a requirement, but I am just cautioning that in the process, you are going to throw out formulations that are clinically probably equivalent.

DR. KIBBE: To ahead, Ajaz.

DR. HUSSAIN: That is one of the reasons, I think, why we pushed the concept of quality by design, and so forth, because all the relevant formulation information and all that has never been brought into that discussion.

It was simply a test to test comparison discussion, so over the last several years, we have brought that discussion up, and then as you go towards understanding your formulation,

understanding what pharmaceutical equivalence could mean from that perspective, we actually can open that debate again because of that.

DR. KIBBE: Ken.

DR. MORRIS: Just a quick question, Jurgen. You are still doing dose-ranging studies when you are doing the initial development, I guess, so if you are going to use the prior knowledge, use the dose-ranging studies, doesn't that help you when it comes time to determine whether or not the tests are over-discriminating or not?

DR. VENITZ: But I mean most of the time, even a two-fold dose range, you may not be able to distinguish clinically, so you are talking about 100 percent difference in formulation performance, and clinically, you may not be able to tell the difference.

DR. KIBBE: Paul has another one.

DR. FACKLER: I just want to correct something. On the nasal products, the clinical study is required, but in addition to that, the

only way to get a generic product approved is to also pass a PK study and also pass in vitro plume geometry and spray pattern.

So, one of those three isn't good enough, two of those three aren't good enough, all three need to pass in order for the nasal products, which, in my personal opinion, is overkill for demonstrating that the two products are equivalent. The clinical study alone should have been enough. If the patients are being benefited equally, the products to some extent are bioequivalent.

The other thing I wanted to correct was just that the variability of mesalamine is admittedly high, but not so high that it can't be dealt with in a pharmacokinetic sense.

DR. YU: At the last Advisory Committee meeting, we had a topic on how to deal with highly variable.

DR. FACKLER: Only that I know there are some relatively new data on some mesalamine products available to the Agency, so that the variability, at least from rectal suspensions, is

defined and was manageable in an BE sense.

DR. VENITZ: Just to follow up on that, you are correct. I mean for the intranasally administered drugs, they have to pass all three. What I would like to see for this in terms of the future progress, would be not to get to that level. If we accept in vitro dissolution as a surrogate of in vivo dissolution, as a surrogate of in vivo bioequivalence, let's stick with it.

If you decide that we don't mechanistically understand enough what is going on and we require clinical study, let's stick with the clinical study.

DR. KIBBE: Thank you, Jurgen.

Anybody else? I see by the clock on the wall that we are running out of time. Have we given you enough guidance on this one to move forward without taking any formal votes? Lawrence wants some more information.

DR. YU: That's correct. Thank you.

DR. KIBBE: He wants to thank me. That's good.

I have on my calendar of events that there is a summary and conclusion, summary remarks, and I have two names, and they are looking at each other like which one of you is going to say anything. I would be happy to just rule you of order and close, if you don't have anything to say.

Go ahead.

Conclusion and Summary Remarks

DR. HUSSAIN: I think again as the previous meeting, I think the discussions were very valuable and I think help us think more. The one I think you probably for the first time got an opportunity to see the range of laboratory and other such activities that we have ongoing, and I think the Critical Path Initiative clearly is not just lab based, it is much broader than that, but that discussion allowed us to think more carefully about how to approach the Critical Path Initiative.

It also helped us to start thinking about how do you align such programs, especially the laboratory programs, to be targeted and the key questions. The challenge is great and I think we

want to maintain as many best practices as we have, and you did see a number of best practices sort of come out in the discussion, and maintain that, and bring all the offices in OPS to be aligned together.

The immediate office project that we articulated, the three projects, all interrelated, I think will be a means to not only identify the best practices, but also to bring a system approach to address uncertainty and complexity, and I think that would be the key aspect and in many ways, that allows us to approach bioequivalence, follow-on proteins, generic drugs, all of those challenges next year in a systematic manner.

So, I think in a number of cases, I think irrespective of what that pathway for these products might be, the follow-on proteins, the scientific framework for the decisionmaking process should be common irrespective of that, and it should be related to the uncertainty and complexity of the dosage form set of products that we have.

At the same time, I think you saw an

impressive array of laboratory research from biology to quality, and how do we align that, I think is a significant challenge. We have sort of summarized that discussion early this morning, and the key questions, the metrics, I think will be the key part for sort of making sure whatever approach we use is measurable and then quantifiable in terms of its benefit to the critical path, and so forth.

But I do want to emphasize in the sense that FDA is only one part of that critical path. Industry, academia, and other agencies play an equally important role. Our role will be more also of coordination, but the need for research, especially fundamental research in this area and need for public funding is acute.

I do want to go back and say the formulation development, manufacturing has been a neglected area, especially in the U.S., and if you don't bring the focus on that, I think we are already 10 years behind Europe and Japan in many of these areas, so we will lost that part of the industry, so that is important, so seek your help

to make that case also.

I think in terms of the gaps going to the desired state, Helen outlined some of the key fundamental organizational gaps. Some reorganization is already occurring. White Oak provides an opportunity to really bring a team approach and peer review process to the CMC function in Office of New Drug Chemistry, but at the same time, I think one key aspect is a question-based CMC review process which focuses on risk.

That is already in the works, but also support that with tools that we have not often utilized in this arena, and that is chemometrics modeling and other aspects of that.

I have a virtual team for chemometrics right now, but I think we are adding people with computational fluid dynamics, and others, to really make a core team that will support the review function in many aspects.

For example, computational fluid dynamics is the issue of hydrodynamics, issue of inhalation

products, and so forth. So, hopefully, we will have that team up and running soon.

I think the science gaps are significant from a training perspective, but those are not, in my opinion, unsurmountable. I think we have seen, we have the expertise within the Office of New Drug Chemistry, Generic Drugs, and so forth. It is simply identifying and aligning that expertise bear on some of those challenges, but also provide a training program for all of our reviewers.

In fact, I really think the PAT training program opened up a lot of opportunities for our staff to excel in areas and become leaders worldwide, and although we cannot do the entire period, training for all of our staff immediately, especially the practicum part of it, but as we go to the next PAT training program, we intend to open the didactic sessions that we have locally to all of CMC reviewers to be part of it. So, we will bring that onboard.

I think Jon outlined for you some of the directions we will make more in policy. Jon is

aggressively moving in that direction and I think his leadership will help us align. A number of people have joined his group. He has a group that is focused on that now.

So, policy alignment and the OPS Coordinating Committee with Gary Buehler and Keith Webber co-chairing that, sort of brings all in one place now to sort of make sure that the policies that evolve are aligned with where we want to go.

The issue I think I do want to mention, the issue of two-tiered approach, I think there is a risk of that, clearly, there is a risk of that, but I think we will try at least at the draft 3.1 for Q8, at least I felt that the language was written not to invoke a two-tiered approach. It's a continuum, it will be a challenge to manage, but I think we will get there.

I am hoping in Yokohama, Japan, starting November 12th, we will bring Q8 to Step 2. I am keeping my fingers crossed. As soon as that happens, I think things will start moving rather quickly.

Pharmaceutical development information is already coming in. Many companies were willing to take the first step, and have done so, and the initial experience is positive, but we will have a quality system, along with peer review process, to make sure consistency and proper utilization of that comes in.

I thin, the other two topics are probably fresh in our minds. I think bioINequivalence is a significant challenge, but it is a challenge right now we are facing to minimize our resources being spent in things which we think are not value added, and I think as we move forward, the discussion here will be helpful.

We will probably not bring that topic back and we will probably come with an approach, and then solve that in a way which is consistent with the way we do it, so I think the discussion will be helpful, but I still feel, I think Jurgan and Professor Nozer Singpurwalla, I think we have to start using prior information, prior knowledge more effectively, and especially with biostudies that we

will have access to, I think it allows us to be more proactive and make decisions more quickly, so that Gary and his staff really don't have to spend so much time in answering these questions in a legal perspective, and so forth.

Locally acting products clearly are part of the critical path for the generic drugs. It is not only GI, inhalation, topical, it is an entire area of research that Lawrence will have to sort of spearhead and move forward, and that is a critical path research for generic drugs.

Approval of generic drugs in a timely manner hinges upon that. I think that PAT concept, the cGMP, the Quality by Design are all positioned right to help generics and help innovators all together, and so you will see that happen.

With dissolution testing, I do want to sort of say that I think dissolution testing, we have to think carefully about the variability aspects of that and how we calibrate. In many ways, I think our labs have started putting a document together. They feel that mechanical calibrators

and others are sufficient and relying on an external calibrator of poor quality actually is diverting attention away and actually creating problems, unnecessary problems, so we will issue something on that soon hopefully.

With that, I will hand it over to Helen.

MS. WINKLE: Ajaz did a wonderful job of recognizing, I think, the contributions that the committee made. I think there were some excellent discussion over the last two days and some excellent recommendations that have been made to us on things that we need to focus on more and areas that we need to do more planning and even more research.

I did also want to mention I thought that the presentations made by Dr. Boehlert and Dr. O'Neill on the two workings groups, the subcommittee for Dr. Boehlert and the working group for Dr. O'Neill, were very beneficial to those discussions. I think both groups are working hard to accomplish a lot and to get answers back to us that are really necessary.

The Manufacturing Subcommittee at the last meeting I thought did an excellent job, and think their report back to you yesterday was indicative of how much effort they are putting in to helping make some of the recommendations that we need to move forward.

Also, with the Dose Uniformity Working Group, they, too, have worked very hard during the year, and I think that the report Bob made was well accepted by the committee and is a good indication of how these working groups, too, can be beneficial to the committee in making recommendations to us in the future.

I do have some other little things, though, I want to talk about, and that is the two people that are leaving the committee. It is a sad time for us, I think here at FDA, because we have appreciated both Marv and Art's contributions. They have been very, very significant in helping direct us at the Agency in the directions that we really need to go, and they have also provided a great deal of scientific expertise and knowledge,

not only on the committee, but in other aspects, too, and they have been very valuable to us.

The one thing, too, I would like to add is they have also added a great deal of humor to this committee, which I think many of us are going to miss. Now, how long we will miss it is questionable, because they are both SGEs and can be called back at anytime--just like Gordon is over there shaking his head--they can be called back at anytime to participate in different discussions, and I think that we are probably going to continue to take advantage of them.

But today, being their last day on the committee, I do want to present them with these plaques in recognition of their service to the Advisory Committee.

The first one is to Dr. Kibbe. Not only has he been an excellent, excellent member of the committee, he has also been a very, very thought-provoking chair even though a little schizophrenic, I worried about today, when he thanked himself. But we certainly appreciate all

your service and everything.

Thank you.

[Applause.]

MS. WINKLE: And the other plaque goes to Marv, and the one thing I want to say about Marv, I have enjoyed having dinner with Marv in the evenings. Last night, for you who weren't at dinner, he had this huge, huge plate of food, and he said, "It is actually bigger than it looks."

He has contributed a lot at this meeting, and we are going to miss him.

[Applause.]

DR. KIBBE: Marvin, would you like to make a comment, a last shot across the barrel?

DR. MEYER: It took I guess 30 years to get on this committee, but I have thoroughly enjoyed it. Everyone around the table brings a different perspective, and that is what makes it good for the FDA and fun to be part of.

We have good chairs, Vince Lee, and then Art Kibbe, and so I would highly recommend this position for three years to anyone who wishes or

gets invited to participate. Beyond three years may be questionable.

So, thank you.

DR. KIBBE: Thank you, Marvin.

I have a whole series of points to make. First, is that this has been a real joy and an opportunity to serve and do what I think are useful things, and to work with people who are dedicated to having positive outcomes for the American public.

Most of that, of course, goes, the blame for how well it turned out goes to Ajaz and Helen, who lead a great ship and have become close friends, as well as good working colleagues.

I think we did quite a bit over the years and I think there is quite a bit more to do, and the committee needs to move forward, and I would be happy to help in whatever manner I can.

One of the things that I think you need to be careful about is that the speed of change is ever increasing, and like Alice, you are running as hard as you can just to stay where you are, and to

get ahead, you have to jump off of that treadmill and get on a different path.

One thing that I didn't mention this morning that you need to keep in the back of your mind is that according to the U.S. law, treaty trumps law. If the Senate and the President want to sign a treaty with some country that allows for something to happen, the Food, Drug, and Cosmetic Act is trumped by the treaty, and whatever rules and regulations you have, the treaty wins.

Yes, it is absolutely true. Treaty trumps law, and the President signs it, and the Senate agrees to it, and the House of Representatives can complain all they want, and the regulatory agent have to readjust.

I would love to see the industry take some of its money that it spends on direct-to-consumer advertising and put it into, first, getting the American public to understand how cost effective drugs are relative to other therapeutic moieties, because they don't understand that, because they see the bill in front of them and they don't see

the other bills.

The other thing is to get them to understand that drugs aren't safe, and they shouldn't just use them because somebody says it might be a good deal. I don't know whether we can get the industry to do that, because I know that the ads are meant to sell things rather than not sell things, and taking out ads to tell people not to do things is hard to get them to do, but I would love to do that.

We need to change the criteria for how we evaluate who well the FDA is doing. I think there is way too much pressure on them to produce new drugs, to produce new reviews, to produce new things, and I don't know what the right productivity criteria is.

I know we need to change the productivity criteria for the U.S. Patent Office, that we have got to stop them from just issuing patents to make sure they have issued three patents, and give them credit for not issuing a patent that shouldn't be issued.

Then, lastly, the goldpost. When you use science to establish the goldpost for regulatory approval, you have moving goalposts because science moves, science progresses, current best thinking is always better than it was 10 or 15 years ago, and both the Agency and the industry have to understand that that is not a threat, that is an opportunity.

I truly have enjoyed myself and I hope that what little I have done has contributed to everybody else having a good time.

I think that it is 4:30 and it is an appropriate time for us to adjourn. If there are not other dramatic statements that need to be made by anyone else, I will see you next time maybe.

[Whereupon, at 4:30 p.m., the meeting was adjourned.]

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