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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE**

Volume II

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P R O C E E D I N G S

**Call to Order**

DR. TAYLOR: I would like to call the committee to order, the Advisory Committee for Pharmaceutical Science.

This morning, for the record, I am not sure the audience has changed significantly, but perhaps we should have reintroductions of the committee briefly with your name and affiliation followed by some announcements from Dr. Somers. We will start with Dr. Branch.

DR. BRANCH: My name is Robert Branch. I am from the University of Pittsburgh.

DR. ZIMMERMAN: I am Cheryl Zimmerman from the University of Minnesota.

DR. DAVIDIAN: Marie Davidian from North Carolina State University.

DR. TAYLOR: I am Robert Taylor. I am from Howard University.

DR. TEMPLETON-SOMERS: Karen Somers, Acting Executive Secretary, FDA.

DR. GOLDBERG: Arthur Goldberg, independent consultant.

DR. VESTAL: Robert Vestal, VA Medical Center, Boise, and the University of Washington.

DR. BRAZEAU: Gayle Brazeau, University of

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Florida.

DR. WILLIAMS: Roger Williams, Center for Drug Evaluation and Research.

DR. TAYLOR: Thank you.

**Conflict of Interest Statement**

DR. TEMPLETON-SOMERS: I would like to read the conflict of interest statement.

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

The purpose of this meeting is informational and it will cover a number of broad topics that will require more in-depth discussion at subsequent advisory committee meetings.

Since no questions will be addressed to the committee by the Agency on issues dealing with a specific product, IND, NDA, or firm, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest at this meeting when evaluated against the agenda. However, in the event that the discussions involve any products or firms not on the agenda for which an FDA participant has a

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financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

Thank you.

For speakers who may not have been here yesterday, we are using a timer to keep everybody on schedule, and you will have a green light when you have plenty of time, a yellow light when it is time to sum up, and a blinking red light when your time has expired.

In addition, if you answer a question or speak in any way, we ask that you identify yourself and please use a microphone, so that it will be picked up for the transcriber. Thank you.

DR. TAYLOR: Thank you, Dr. Somers.

The morning session is Chemistry, Manufacturing and Controls Topics.

The first speaker is Dr. Steve Moore, who will discuss Biotechnology Products and Pharmaceutical Equivalence.

Dr. Moore.

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**Chemistry, Manufacturing and Controls Topics**

**Biotechnology Products: Pharmaceutical Equivalence**

DR. MOORE: First, I am glad to be here today to talk to you about biotechnology products.

[Slide.]

I am talking to you as the Chair of the Biotechnology Technical Committee, which is under the CMC CC.

[Slide.]

There is quite a number of recombinant DNA products that CDER regulates, and I have a list here of ones that have been approved for marketing. According to an intercenter agreement, CDER regulates certain drugs and antibiotics including hormones, and a lot of these are, in fact, hormones.

One of the first or actually the first recombinant DNA product approved was approved in CDER. That is the human insulin. There are two manufacturers for human insulin, as you know, are Lilly and Novo. They use different host cells to produce these insulins, and the insulin molecule has A and B chains and 3-disulfide linkages.

A recent addition to this list of insulins is a humalog lispro, which has a change of the amino acid

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sequence at positions 28 and 29 in the B chain, and the result of that is a faster acting insulin. The other insulins that you see are formulations for different times of action.

Then, there is also a human growth hormone. The first one was 192 amino acid long because it had a methionine which is put on by the bacteria, and the remaining ones are 191, which corresponds to the exact length of the human sequence. These molecules have 2-disulfide linkages in them.

The last one I am showing there is the human beta-glucocerebrosidase analogue known as Cerezyme by Genzyme, and this is the most complex recombinant protein that we have, 497 amino acids long. It is heavily glycosylated, and there are multiple disulfide linkages.

To add to the complexity of this, the glycoprotein chains are modified to expose mannose residues and the purpose of that is for targeting to mannose receptors on macrophages, and the enzyme is for the treatment of Gaucher's disease, to reduce the sphingolipids inside the cells.

[Slide.]

I would like to talk to you a bit about the Biotechnology Committee. We give guidance on a number of

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areas of biological type molecules, rDNA proteins primarily, but there are also other products which fall under this category, synthetic peptides and oligonucleotides, and most recently rDNA metabolites -- and I will speak about that a little bit later -- and monoclonal antibody reagents, and recombinant DNA enzyme reagents, and other products that may be put before the committee.

We are engaged in development of guidance documents and we answer inquiries both from inside FDA, primarily from reviewers who have biotech, biological drugs under review, and also from industry for new products and new ways of doing things.

I am the Chair, as I said. The Vice-Chair is Duu-gong Wu. We both came to FDA with hands-on experience in recombinant DNA technology and molecular genetics.

The members we have chosen to represent widely the divisions of CDER, there is Liang Zhou, who has experience in monoclonal antibodies and peptide drugs, and Euginia Nashed, who is experienced also in monoclonal antibodies and ELISA technique. Rao Kambhampati, who has experience and expertise in oligonucleotides. Brenda Uratani, who formerly worked at a small biotech firm, and she is from Peter Cooney's group in Microbiology.

There is also Brian Nadel. He is a field

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inspector and has expertise in large-scale fermentations. There is also Meade North, who is an observer from Compendial Operations.

[Slide.]

Under the Biotechnology Technical Committee, BTC, there is a number of working groups. One such active working group currently is working on rDNA reagents, and they are currently working on monoclonal antibodies used as reagents. Their task is to develop a guidance on the use of these biotechnology-produced monoclonal antibodies as reagents in drug manufacture.

Several points there. There is a current guidance for therapeutic monoclonal antibodies, a PTC that CBER has, but it is not considered to be suitable since these are, in fact, reagents, and not intended to be injected into humans. These are used non-sterile. There are other issues that are different from the way that monoclonals is used as therapeutics, and that being that these are generally bound to a solid support and used during the purification of the drug substance.

There are also some of the same issues, such as viral validation, however, even here, the monoclonal antibody is usually used in a column which is upstream in the purification process, so you would also have to count

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the downstream steps and include it in viral validation studies.

The Chair of this subcommittee is Euginia Nashed and these are the members. We have members from OGD and ONDC. Also, there is a representative from CBER, who is coordinating the same kind of document that CBER is trying to develop.

[Slide.]

Another working group under the BTC is R-DNA Cellular Metabolites Working Group. Manufacturers are interested in using metabolites, such as antibiotics, amino acids, vitamins, et cetera, made by rDNA techniques. They wish to do that because they are able to increase the yield such as increasing the promotor coding for a gene, which eventually codes for an enzyme that the cell uses in its machinery to manufacture such a metabolite, or they may want to change the copy number and increase the number of gene units.

There is a CBER/CDER joint Points to Consider in 1985 for recombinant DNA proteins, but we also consider that to be nonsuitable, consider it to be too restrictive because the product here is a low molecular weight organic molecule that can be readily characterized versus proteins, and also that former document contains extensive details on how to

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characterize cell banks and characterize the protein with respect to structure, disulfide linkage, et cetera.

So, also we think that these small molecular weight metabolites would be easier to purify away from other protein contaminants, which is a major issue in the PTC.

The Chair here is Duu-gong Wu, also a member of the Biotechnology Committee, and these are the members.

[Slide.]

I would like to give you now just a bit of a summary on the update of the status of some of these documents that we are working on.

The monoclonal antibodies guidance. That has gone through the Biotechnology Committee review. As we go in steps, we conceptualize these things within the committee. We send them out to working groups, and the working groups develop drafts, send it back to the BTC, and we discuss it and go back with your comments and say you need more work, then, come back and finally before we forward it on for more general circulation inside FDA, and then hopefully, finally, it gets published in the Federal Register. We are hoping to get that one out this year.

There is also the one, the metabolites guidance. That one has gone through final round within the Technical Committee, and hopefully, can get that one out this year,

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soon.

Right now we have planned oligonucleotides guidance. Right now Rao -- not very many people can say his last name -- he is an expert on the oligonucleotides area, and he is the chairman of a working group on that area. Right now we are advising sponsors of INDs to follow our publication in 1993 about the regulation of oligonucleotides.

We are also planning a guidance on rDNA enzymes. Manufacturers are very interested in using rDNA enzymes since they would like to move away from animal source for using reagents in purification steps that come in direct contact with the drug substance.

One of the main reasons here is the bovine BSE, possible contamination from bovine enzymes sources, and also for porcine viral issues there.

Also, members of the Biotechnology Committee work closely, including Yuan-Yuan Chiu with Gene Murano, who is the co-rapporteur for a Q6B for specifications and tests for biotechnology products. That ICH document is now in Step 1 or a little bit beyond.

I am going to skip over the next category and go to a comparability protocol. This is something that has been submitted for the Biotechnology Committee to look at

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and discuss. What a comparability protocol is, if you haven't already heard of one, is a plan on how a company might undertake the steps to make a change, and then what tests, et cetera, they will use to prove that that change has no deleterious effect on the product.

This is very familiar to industry. They refer to them generally as a change protocol. They write up SOPs before they make a change, and it goes inside for clearance before a change is ever made.

The FDA, at least the reviewers are not use to seeing these kind of protocols. We are used to seeing the end results after all the data has been collected and to show what the change was and that the change did not affect safety and quality and efficacy of the product.

The idea is that if a company can send in a protocol and have it approved, like a supplement, that this could reduce the burden of time that they are waiting to implement the change.

There is proposals for biotechnology products in our harmonization efforts with CBER, that we will have three tiers for the time periods that are needed to wait for approval of supplements. The idea of the comparability protocol is to reduce the tiers down one level from perhaps a prior approval supplement down to a supplement that can be

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implemented in 30 days, a CBE, or a CBE-type supplement down to annual report.

I would like to go back now to the pharmaceutical equivalence documents which are being discussed and planned within the Biotechnology Committee. Dr. Yuan-Yuan Chiu would like to comment and discuss various aspects of pharmaceutical equivalence as it applies to biotechnology products.

[Slide.]

DR. CHIU: I have been asked to address the issue of pharmaceutical equivalence. I will be very brief.

[Slide.]

Pharmaceutical equivalents is defined in the Code of Federal Register. It is stated, "Drug products that contain identical amount of identical active ingredient, i.e., the same salt or ester of the same therapeutic moiety."

Therefore, in order to show two drugs products are the same, the prerequisite is the two products contain the same active ingredients or the active therapeutic moiety. For purified organic compounds or inorganic compounds to demonstrate sameness is pretty straightforward because with available analytical techniques, however, when we address the biotechnology product, biological drugs, it has

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complexity of the product and also because sometimes they are quite impure, they are crude extracts, therefore, to demonstrate sameness, it becomes quite complex.

[Slide.]

There are different occasions one needed to demonstrate the sameness. One situation is you have multiple companies or multiple suppliers or you have generic drugs or innovator drugs, you want to show the pharmaceutical equivalence across the product. Then, you need to demonstrate sameness.

The other situation is when one makes manufacturing changes during IND stages or post-approval, then, you may want also to show the sameness.

So, to address the issue of this problem, in 1996, CDER and CBER issued a joint guidance document labeled as an FDA guidance concerning demonstration of comparability of human biological products including therapeutic biotechnology products.

This document provided the framework how to compare different products including all drug substances, however, they only provide sort of a hierarchy of testing, so if you make -- and this guidance document also only address the manufacturer's changes, not address when you have different firms to make a product.

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So, it give you sort of decision. If you make a manufacturing change, and the first level of testing is physical, chemical, and biological testing to show whether the product has now changed up to the manufacturer change.

If that shows differences or if that doesn't give you conclusive evidence, then, you may want to go to the second level. That would be animal PK/PD, and then if that is not enough, then, you may go to clinical level and the PK/PD or even comparative clinical studies.

So this document only provide that kind of information, and doesn't address how do you demonstrate the pharmaceutical equivalence related to the sameness of the active ingredients.

Therefore, we felt there is a need to do this.

[Slide.]

Because of that, we look at all the biological drug substances we have in CDER and CBER. So, we come up with this list. This list is in order of the complexity of the molecules. We started with recombinant DNA antibiotics and cellular metabolites, which Dr. Moore has mentioned briefly. They are small molecules, so they are pretty straightforward to demonstrate sameness, and the documents, Dr. Moore mentioned it has a section on pharmaceutical equivalence.

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The next level of complexity would be synthetic peptides which could include the linear therapeutic peptides or it could be more complicated, and multiple antigen peptides used in vaccines.

So, we think, you know, we would like to address the issue of pharmaceutical equivalence of all different types of products, and we will start now with synthetic peptides.

[Slide.]

In 1994, in November, both CDER and CBER also issued a guidance document for the submission of chemistry, manufacturing, and controls information for synthetic peptide substances.

This document does not address the pharmaceutical equivalence issue. It only address the characterization, the preparation of synthetic peptides, and mainly address the therapeutic peptides, the relative simpler ones.

The ICH document is for drug substances and therefore traditional pharmaceuticals or for biotech products, do not address synthetic peptides either. All those documents under the scope, the synthetic peptides are waived, are not included because the synthetic peptide really is a hybrid of biotech product and the synthetic organic compound. So, it has different characteristic to

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either one. Then, you have some common characteristics to both of them. So, they are sort of unique.

[Slide.]

Our goal is to revise this document and to include a section to address pharmaceutical equivalence. We have recently reconvened the previous synthetic peptides working group and added new members. We have members from CDER and CBER, and those people have expertise in therapeutic products, in vaccines, diagnostic kits, therefore, we think with this group of people we will be able to revise this document and to suit the needs of the Agency and the industry.

Then, you will hear from the two co-chairs to discuss scientific issues revolved around synthetic peptides.

DR. TAYLOR: Thank you.

The next presentation will be on synthetic peptides, and it is Dr. Niu and Dr. Berkower.

### **Synthetic Peptides**

[Slide.]

DR. NIU: As mentioned by Dr. Chiu, synthetic peptide is one of the biotech products. Today, my talk only deal with synthetic peptide that have well-characterized structures, and Dr. Ira Berkower will discuss with you the

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other aspect of the synthetic peptides.

[Slide.]

The synthetic peptides, the synthesis of peptides have two ways to synthesize the peptides. The first is solution-phase method. Second is solid-phase synthesis method. The general principle of this synthesized peptide by both solid-phase synthesis and by the solution-phase synthesis is identical.

The amino acid have free carboxy group, is linked to the amino acid, free amino group with coupling reagent to form amide bond of peptides as shown in this slide.

[Slide.]

In the solution-phase method synthesis, the different size also of peptides can be achieved by coupling the various short peptides, such like dipeptide or tripeptide to form a large peptide with a coupling reagent and under the controlled temperature.

The advantage of this three-phase method is first you can get the homogeneous product, but because every intermediate, such like a dipeptide or tripeptide can be purified either by crystallography or by pass-through sincogal [ph] column, and there is a second, there is large quantity of the peptide intermediate can be obtained.

The disadvantage of the solution-phase synthesis

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is, first, it is time-consuming to purify all the intermediate peptides. The second, sometimes it is very difficult to dissolve the intermediate into the organic solvent.

[Slide.]

In the solid-phase synthesis, the first amino acid is coupled to the polymeric resin, and then the N-terminal blocking group is removed, and then second peptide is coupled to the peptide resin by the coupling reagent. So, the desired peptide of all the amino acid has been linked to the peptide resins by the repeating process.

After the completion of the synthesis of peptide, a reagent is applied to remove the chain from the resin, and to liberate the peptide, finished peptide into a solution, the solid-phase synthesis offers several advantages over the solution-phase method.

The first one is elimination of the solubility problems. The second is solid-phase synthesis offers a relatively short synthesis time. The disadvantage of this solid-phase synthesis, the first racemization has occurred during the coupling. The second is the deletion peptide is caused by the incomplete removal of the N-terminal blocking group, the swelling of the peptide resin B.

Number C is modification of peptides, which will

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be discussed by Dr. Berkower.

[Slide.]

After the completion of synthesis of the peptide, the crude peptide may contain the following by-product. The two most important ones are racemized peptides. That means L-amino acid and racemized to D-amino acid during the coupling.

The second is deletion peptide. These two peptides are most important in the contamination. So, we need to purify the crude product away from the by-products, and usually we use HPLC to remove those by-products.

[Slide.]

After you have got your purified desired peptide, then, you need to characterize your peptide. The minimum requirements for this structure characterization of the peptide include the following: first, it is amino acid analysis; second is mass spectroscopy; third is peptide sequence; the last is peptide mapping.

The amino acid analysis provides evidence for the amino acid composition in the peptide, and also can provide information for the content of the peptide in the sample.

The mass spectroscopy can provide the information on the weight of the peptide and sometimes can give you the sequence information. The peptide sequence can be useful

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determination of correct sequence of the synthetic peptide, and also provides a good estimation of homogeneity of the peptide, and to detect the deletion peptide in the product.

The last one is if a peptide contain more than 20 amino acid, the peptide mapping may be necessary. The last one is using the chromatographic analyzer, you can determine the purity of the peptide, as well as determine and monitor the impurity profile from the peptide.

The last one is biological activity may be needed with in vitro or in vivo test whenever it applicable.

I finish my talk. Thank you.

[Slide.]

DR. BERKOWER: Good morning. I am going to be discussing the application of peptides to make peptide vaccines. This is just one of the areas in which a very beautiful and well-characterized peptide may have to be modified in order to take that structure and make it into a useful biological function.

[Slide.]

In this talk, I will be discussing, first, certain features of the peptide vaccine that are essential in order to elicit an immune response, which is the purpose of the vaccine. The immune response depends on the interaction and collaboration between two types of cells, B cells, which are

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the cells that produce antibodies, and T cells, which are the cells that provide essential helper functions needed by the B cells to go on and produce the antibody.

As stated in this slide, a good peptide vaccine should ideally have antigenic determinants or we called them epitopes targeted toward each kind of cell. That would be a T cell epitope recognized by T cells, and a B cell epitope recognized by the B cell that is going to make the antibodies.

In my little talk, I will be giving two specific examples of peptide vaccine constructs. The first would be a more or less classical peptide protein conjugate in which a peptide is conjugated to a protein, and the protein carrier provides the T cell epitopes.

In these conjugates, heterogeneity is a well-known feature and I will be demonstrating that. The second example is going to be the multiple antigenic peptides or MAPs. These tend to be tetrameric structures which contain both T cell and B cell epitopes. I will illustrate an example of difficulty both in analyzing and actually in synthesizing a peptide of this type.

[Slide.]

This slide shows a cartoon of our current understanding of how T cells and B cells work together. The

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top right corner of the slide shows an antigen which has two parts. This could be a synthetic peptide. The triangular part is the part recognized by the B cell, the B cell epitope. The rectangular part is the T cell epitope, and they are linked together. They must covalently linked together to work together.

The top left corner, we see the B cell that is getting ready to respond to the antigen, and the key feature of this B cell is a surface receptor that is nothing other than the immunoglobulin that the B cell will later make as an antibody, and that becomes the receptor, as you can see, for receiving the triangular part, the B cell epitope of the antigen.

That happens first. In the second step, the B cell internalizes the peptide and partially degrades it into fragments, and then as shown in the bottom, presents that on its surface in the binding group of a second molecule called the MHC molecule, major histocompatibility complex molecule.

It turns out that the T cell shown on the right has a receptor that sees this combined determinant, that is, the peptide, the foreign peptide with the self-image seen together, and that is what triggers the T cell to release various interleukins shown here as IL-4 and IL-5, and there are other helper effectors, as well, that the T cell

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provides back onto the B cell, which stimulates it to make antibodies.

So, to get an optimal antibody production in the bottom of this slide, you need both a T cell and a B cell epitope ideally in your peptide. I am going to show now specific examples. The first example was when the B cell epitope, the triangular part is the peptide, but the rectangular part is an intact protein, and that is shown on the next slide.

[Slide.]

This is a little faint, but what I am showing obviously are peptide B cell epitopes in red attached to a wavy protein shown in black. What we tend to know about these peptide protein conjugates is the ratio, the coupling ratio shown on the left margin.

For each row I have shown a different ratio. In the top, a ratio of 3 to 1, in the middle 2 to 1, and the bottom 1 to 1 ratio of coupling, and what I am illustrating in this slide is that when the ratio is 3 to 1, there are many ways to get 3 to 1 including some 3's, some 4's, and some 2's.

When it is 2 to 1, if there were three main sites that were targeted, there are still many ways to put two peptides onto three sites. When it is 1 to 1, again, there

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are many ways to put one peptide onto three sites.

In fact, on this entire slide of nine possible structures, there are only two that are actually the same, seven are different. So, we see quite a bit of heterogeneity, and if we only know the average number, say, for the whole slide, which of course would be a mixture of 3's, 2's, and 1's, coming out to a ratio of 2 to 1, in fact, we might have nine different actual molecular components.

This is not a big problem if all the components work equally. It could be a big problem if the 1's were not immunogenic, if the 2's were ideal, and the 3's were overmodified, for example. So heterogeneity is a well-known problem that has to be dealt with in these types of structures.

[Slide.]

The second example I would like to give is called the map peptide. What is shown on the top is a typical linear peptide that would be synthesized as a monomer, but in the second row, the dimeric map occurs when the first lysine in the structure is not blocked at its epsilon immuno group, so the next growing chains grow off both the alpha-immuno and the epsilon-amino, giving a branch, and then if the synthesizer is just allowed to run, the chains will grow in parallel, forming a dimeric map.

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If we do this with two branch points, we get a tetramer, three branch points give an octomer and so on. Tetrameric maps are the ones that we see most commonly, and that is in the middle of this slide.

[Slide.]

Now, I will give a specific example of a map. This would be one way to make an AIDS vaccine perhaps. What I am showing on the top of the slide is a schematic of the AIDS envelope protein GP160, which of course can be broken into GP120 and GP41, and let's say we knew that a B cell epitope, shown in white, marked B, that antibodies to that site would neutralize the virus.

Let's say we knew a T cell epitope, marked T and shown in black, was a good site for helper T cells, and we might imagine putting those two together in a single linear chain of B and T, and then linking that into a map, as shown in the middle right of the slide. So BT map 4 means the B cell epitope is to the left, the T cell epitope is to the right, and four of them are linked together in a map.

In comparison with that, we have just the B cell epitope on the left, where it is just the B cell map, 4 B cell epitopes. The difference is shown in the bottom of the slide here, versus here.

On the left, the antibodies, of course, made

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against just the B cell map are very low, while the antibodies on the right, against the B and T map, are 100 times greater.

[Slide.]

However, maps, although they might be very desirable from an immunologic and functional point of view, can in fact be quite complex, and I will just illustrate that in two slides quickly.

The first slide shows a monomeric peptide, synthesized corresponding to a malaria sequence. This is a 31-mer, and when analyzed by mass spec, it shows basically a single component with a little bit of a side shoulder. In comparison with that, we have a map made of roughly the same sequence. As you can see, it is an incredibly complex pattern.

If you look at the legend, on the number of peaks the computer detected 16,000 peaks in this sample, so it was impossible to assign a single species to this. In the last slide I would like to show why we think this may happen.

[Slide.]

This is a map more or less like the first tetramer that I showed two slides ago. On the top you see that there is a tetramer linked in this case to four palmitic acid residues to give it a lipid tail. In the bottom is the

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point. I am showing a space-filling model with the lipid tail pointing down and the map part pointing up, and what I would like you to appreciate is that it is kind of crowded at the top, that there is a lot of potential for steric hindrance. What we think goes on with maps is that as the four chains try to grow, chains 1 and 2 might hinder 3 in one step, 1 and 3 might hinder 2 in another step, and 2 and 3 might hinder 1 in another step. So, as a result they are incredibly heterogeneous as they grow.

So, we have a difficulty with maps in analyzing them, because they are complex, but really, that comes from a difficulty in synthesizing them in the first place because of the potential for steric hindrance.

On the other hand, this is in the real world. Maps might be very desirable because they seem to be very potent immunogens and a very desirable way to make the bridge between a nice synthetic peptide against very precisely defined epitopes, make the bridge of that into something that is also very immunogenic and potent as a vaccine.

DR. TAYLOR: The next discussion will be Bulk Active Compound, post-approval changes (BACPAC). There are three speakers: Dr. Srinivasachar, Duffy, and Byrn.

### **Bulk Active Compound**

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## Post-Approval Change

DR. SRINIVASACHAR: Good morning.

[Slide.]

I am currently Chair of the CDER Drug Substance Technical Committee and this morning I will briefly introduce the topic of post-approval changes in the BACPAC substance.

The agency has long realized that even after approval to market a drug, industry often needs to make changes in the processes for manufacture of the drug, and this is particularly true in the drug substance arena where drugs substances which are made by synthetic sequences, these sequences are constantly changed to optimize processes for environmental or economic reasons.

So, there is a mechanism within the Agency to address such post-approval changes.

[Slide.]

I just going to briefly give you what the current regulations are regarding post-approval changes. The industry has to establish with the Agency the changes and describe the changes in full detail.

[Slide.]

Currently, there are three mechanisms for filing the change. They can be filed by supplements or in an

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annual report. Within the supplement area, there are two kinds of supplements - prior approval supplement where the industry informs the Agency of the change and provides data to support the change prior to implementation of the change, and there is another kind of supplement called CBE or changes being effected supplement, where industry can make the change at the same time or even before they file a change with the Agency.

Finally, there are certain changes which can be made in an annual report.

[Slide.]

There are some details of what changes fall into which category, and 21 CFR 314.70 addresses such changes. For the drug substance they are listed on this slide. I am not going to go through this whole scheme here. Rather, I would like to point out that for the drug substance, most of the changes currently fall under the category of prior approval supplements.

Also, it is important to note that the current regulations do not distinguish between changes made at various steps in the synthetic sequence. It could be made at the beginning of the synthetic sequence or toward the final drug substance itself.

Industry has voiced concern that the current

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regulations cause lengthy delays in implementation of much needed changes and is a disincentive to making innovative changes.

[Slide.]

In order to address these concerns, the Agency has decided to develop a guidance document called BACPAC. This is an acronym for bulk actives post-approval changes, and basically, it is a consequence of the REGO initiative. The plan here is to try to focus on areas where the regulatory burden could be reduced for industry, and this guidance document is going to be a guide for changes in the manufacture of bulk drug substances and will be addressed to sponsors of NDAs, ANDAs, Type II DMFs, and so on.

[Slide.]

Right at the outset, I think everyone is agreed that a guidance of this sort should be based on sound scientific principles, and we have basically looked at ways of addressing this.

One way is, of course, like the SUPAC documents, which you may be familiar with for the finished dosage form. There was a research component to that, and a similar possibility exists also for bulk drug substances, however, this is a very complex area and I believe only certain aspects can be addressed through research.

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As you have heard, we have an initiative called the Product Development Research Initiative, which will try to focus on some areas where research is needed in support of a guidance of this sort.

In addition to this, there was the realization that a lot of the research work has already been done by industry and that there is a lot of data that industry already has regarding changes in bulk drug substances.

[Slide.]

In order to address those issue, we decided to initiate a workshop, which will be a starting point for the guidance document. An AAPS/FDA-sponsored workshop was held in March in Arlington.

[Slide.]

The objectives of the workshop are listed here and on the next slide, too. Basically, this workshop was intended as a mode for industry to present their experiences on bulk drug changes and to exchange information with them.

[Slide.]

The major sessions that were addressed at the workshop are listed on this. Basically, they fall into two categories: assessment of changes, how industry assesses various changes they intend to make, as well as various types of manufacturing changes.

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[Slide.]

A central concept that emerged at this workshop was the concept of sameness in the presence of a change, and basically, the two criteria that are most important for determining sameness after a change are the impurity profile and physical properties.

[Slide.]

It was generally agreed that impurity profiles could be addressed through the various ICH guidances that are now available for impurities in drug substances, as well as residue of solvents, and also USP has recently come up with another impurities monograph, which also addresses this issue.

So, these could be used as a basis for assessing the impurity profiles. There was a general agreement also that impurity profile is important all across, through a synthetic sequence. In other words no matter where a change is made, one of the major consequences of that would be on the impurity profile of the drug substance.

[Slide.]

Another very important aspect of the workshop was this concept of a true solution. This is where, since most bulk drug substances are solids, either crystalline or amorphous, there is a stage in the synthesis where

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everything is in solution and the final drug substances isolated from that solution as a solid.

This solution point could be taken at the point where one can separate physical properties from other criteria like impurity profiles, because in solution, of course, any memory of previous properties is erased, so the physical properties of the drug substance are determined by the change that is present in the final solution, as well as any processing that takes place after that, like milling, drying, and so on. So, this is an important concept that emerged and one that enables us to separate physical properties from impurity profiles, and physical properties need not be evaluated in changes that are made in intermediates prior to the final drug substance.

[Slide.]

Some other concepts that are useful in organizing the document are listed on this overhead here, and they are that there was general agreement that one way of categorizing or organizing the document would be to consider the step that produces the final drug substance and lump all the steps that come before that, prior steps, as another part of the document, in other words, separated into two stages, early steps in the synthesis and the step that produces the final drug substance.

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Industry felt that they make a lot of changes in the early steps of the synthesis, and this is where the major impact of the document is going to be, and that the Agency should address early changes in the synthetic step, because this is where the highest volume of chemicals is involved, and this is where the highest reward for industry is, as well as the lowest risk both for industry and the Agency in terms of impact on the final drug substance.

Finally, a decision tree approach was considered to be very useful, and the document, it was felt, should adopt a data-driven approach for evaluation of a change.

[Slide.]

A more detailed version of these concepts that I have briefly discussed here will be available in the workshop report. I would like to caution that the report does not represent consensus between the Agency and industry. Rather, it is the kind of agreement that industry came to between themselves as to what issues are important for the BACPAC document to address.

Finally, the next stage in going forward in this guidance document would be to form a core working group to actually crack the document, and we have decided that the working group is going to be formed from the current members of the Drug Substance Committee.

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Dr. Steve Byrn is going to follow this up with some other details of various concepts at the workshop.

[Slide.]

DR. BYRN: Eric Duffy and I talked, and we decided that there wasn't enough time for both of us, so Eric is not going to be speaking today. Eric is over here. I would like to introduce him. He is the Vice-Chair of the Technical Committee on Drug Substances at the Agency, and could just as well have given this talk.

[Slide.]

I just wanted to talk briefly about this concept of sameness that has already introduced twice, by Dr. Chiu and also Kasturi. One way to think about this question is from an academic perspective. A professor gives a student two bottles of drug substance, made by different routes, and they ask are these the same, are these substances the same.

One thing to realize that is an issue in our field is that sameness is not always defined by the drug substance specifications, because sometimes these specifications -- most times -- were written early on in the NDA process, and may not be reflective of the actual situation. Also, several of the specifications are older, and some people in industry, many don't want to set a lot of specifications on the drug substance if they don't think they are relevant to

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its performance.

Also, the issue of sameness is sometimes not defined in the monographs, in the USP monographs, for example. Some monographs will not address physical properties at all, so that issue is not defined there.

Although we are not sure, especially for old drug substances, it is probably not defined in the DMF. So, most people are thinking about sameness in terms of 1997 methods of identifying sameness, not, say, 1980 methods. This is an issue that we are going to have to tussle with as we develop this.

[Slide.]

I want to briefly talk -- Kasturi talked about physical-chemical attributes -- I want to briefly talk about impurities because as new drug substances are made, maybe by different routes, for example, because there are patents on a given route, so a generic company may not be able to follow that route or a drug supplier, so they might follow a different route.

We are going to be introducing new impurities, but not above the tenth of a percent level. This whole issue of impurities is an important one, and this is something that the committee does need to realize is, as BACPAC proceeds, we are going to be introducing new impurities.

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The level that has been taken, as Kasturi said, is the level from the ICH, no new impurities greater than a tenth of a percent. This issue is something that a lot of people are concerned about and was raised yesterday by Dr. Walkes.

[Slide.]

This is a flow chart that we wrote to sort of signify how the committee and the conference, the BACPAC conference was thinking about dealing with the issue, and I know it is relatively small, and I am just going to read through this and sort of try to give you a picture of how we are thinking about this whole process.

We want to make a change in something to do with making the drug substance. It can be a process, it could be modern equipment that is more energy efficient. It could be we want to move to a new site, we are going to move our manufacturing to a new site, or we may want to change one of the steps that is dangerous or has environmental problems.

The first question that we ask is this an early step in the drug synthesis or the last step. An early step, as Kasturi said, is where most of the money is spent because a typical drug synthesis may be five steps, and you start with a large quantity at the start and then at each step you lose some of it along the way. At the end, you may have a

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small quantity. So, most of the chemistry is done in the early step and most of the expense.

So if it is an early or mid-step, then, the first thing you ask about is the impurity profile, does it have an equivalent or better impurity profile. If the answer is yes, a change at this point would be of low concern and this is simply an idea, this is not agreed on at all, and as Kasturi pointed out, that would go in the annual report.

If it does not have an equivalent or a better impurity profile, then, we ask does the impurity carry through to the final drug substance. There is a chance that impurities early on will be carried through. They are minimized, but there is a chance. This illustrates our concern with impurities. If it is not carried through, that means you have very good purification processes, then, again, it is low concern. If it is carried through, then, there is high concern and there would be a lot of concern and many companies would not even contemplate doing such a change unless it was absolutely necessary.

Now, you go over here to the last step, then, you first check the impurity profile. If it is not the same, it is of high concern and further work. If it is the same, then, you deal with the physical properties, the flow, the electrostatic properties. If they are the same, then, the

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whole change has low concern. If they are not the same, there is high concern.

Let me just conclude with one last issue, which is this issue of use test. There is a major controversy among scientists in the field as to whether, if you go through this whole flow chart, everything is the same. The student says these two substances are the same. Do we need to do a use test? That would mean make it into drug product, and do we need to, for example, do a stability study on it to see if that product is stable.

The analytical chemists are saying no, it is the same thing. The formulation scientists are saying yes, we don't really know whether it is the same unless we make it into drug product and test it further.

Most large companies said they would -- even though it came all the way through, even if we changed all the regulations to say annual report -- most large companies said they would do a use test to protect themselves from any potential recall issues.

The concern would be maybe with smaller companies or companies that aren't as well developed, whether that would happen in those environments. So, this whole area of use test is another area that we are going to be working out in this area. Probably I should stop.

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DR. TAYLOR: Thank you.

You have heard the discussion of the chemistry, manufacturing, and controls topic. Time now has come for requests for any open public discussion of these issues.

#### **Open Public Hearing**

We had no requests prior to this meeting for discussion of these topics, but if there are individuals in the audience that would like to discuss them, now is the time to do that.

[No response.]

DR. TAYLOR: If not we will move on to the discussion of the issues by the committee.

#### **Committee Discussion**

Are there any discussions by the committee? Yes, Dr. Zimmerman.

DR. ZIMMERMAN: I had a question. I guess it would be for Dr. Moore. How is it determined that a biotechnology product will come to CDER rather than CBER?

DR. MOORE: There is an intercenter agreement developed between CBER and CDER in which it was agreed upon which classes of drugs would be regulated by CDER and which would be regulated by CBER. Basically, CDER regulates organic synthesized drug products, hormones, and antibiotics, whereas, CBER regulates blood products,

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vaccines, monoclonal antibodies as therapeutics, et cetera.

DR. ZIMMERMAN: It is my understanding that the profile of the scientists at the two different agencies are quite different, and some of the issues that would normally be handled in CDER come up in CBER, but are not handled the way they would be handled over here.

I have heard concerns expressed from my colleagues in industry that the reviews are not handled in the same way. There are issues that are not handled in CBER that would be handled in CDER, and because the product goes to CBER, they are not being handled the way they think they should be handled in if they had been in CDER. Am I clear?

DR. MOORE: I know that in this past year, there has been great effort devoted to harmonization of the way that CDER and CBER review and inspect the manufacturers that produce certain products which we call the well-defined biotechnology products.

Now, outside that area, yes, there are great differences, of course, there has to be because those are traditional biologicals as compared to drugs as CDER handles them.

DR. TAYLOR: Dr. Williams.

DR. ROGER WILLIAMS: Dr. Taylor, I would say one of the people in the audience who has had a lot of

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experience with this attempt at harmonization between the two centers in dealing with these products is Dr. Chiu, and if she would be willing, maybe she could give a brief update on that status.

DR. CHIU: In the past, the industry perceived there is a difference between CBER and CDER to approach by technology product regulatorily or administratively, and occasionally scientifically, but I will say scientifically even in the past, the two centers actually treat them quite the same.

Because of the differences in administrative and regulatory, it was the Agency's great effort to bring the two centers into harmony. If we want to harmonize internationally, we must harmonize within Agency.

So, in 1994, under Vice President Gore, REGO, the topic was to make the biotech product to be consistent in the two centers. So, I was involved in that project and I worked with CBER, and we have actually, in 1994, issued a series of documents, guidance documents, also revision of regulations, so now I would say for well-characterized in CBER, they call the specified product, which includes therapeutic, recombinant DNA product, we are more or less the same.

For example, in the past, the biotech product in

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CBER was certified, so it was licensed. Therefore, every batch of the product need to be submitted to CBER for certification before it can be released. The batch process was deleted. It is no longer there anymore.

The most important areas we harmonize are two. One, we work on the prior submissions, so-called the filing requirements, we issue a document called the content and format for submitting documentations for biotech products, and that content and format is the content and format of an NDA for biological drugs.

So, therefore, both CBER and CDER use the same content in the format now. The second thing is we are trying to harmonize post-approval changes, manufacturing changes beyond the stage of post-approval. We have proposed regulations last year. In the past, for biological biotech products, for changes require always prior approval submission, and the proposal now would be also, as Dr. Moore stated earlier, it would be three tiers.

Certain changes would require prior approval, certain changes would be changes being effected, and then certain changes will be annual report, which would bring CBER's biotech products in line with CDER's biotech drugs.

So those two areas actually plus the certification, so the three areas, the major difference is

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now or will be harmonized.

DR. TAYLOR: Dr. Vestal.

DR. VESTAL: I think this question may be more directed to Dr. Williams. I am just a little confused as to how the biotechnology fits into the overall structure that you presented yesterday.

I notice, for example, there is no specific designation for biotechnology. Say, for example, under the Office of New Drug Chemistry -- and I think this follows up maybe a little bit to some discussion yesterday -- is there any plan to create a separate place for biotechnology within the organizational structure?

DR. ROGER WILLIAMS: In terms of science and policy, I would say we are handling it via CMCC and the Biotechnology Technical Committee that Dr. Moore heads. As you can see, we are reaching out to CBER, and we are delighted to have people like Dr. Berkower help us to come to common approaches.

Will there ever be a special review division for biotechnology products? I would tend to say no, although I think many of them are reviewed in 510, just because they are hormones, which is where Dr. Sobel is. As a matter of fact, Dr. Moore works there, and I think Chien-hua, you work there, and Dr. Chiu worked there, too, before she became

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Deputy Director in the Office of New Drug Chemistry.

DR. TAYLOR: Dr. Edeki.

DR. EDEKI: I just have a quick question about some of the biologic products that were presented earlier on. The human glucocerebrosidase analogue for treating Gaucher's disease, just a point of clarification, is that an orphan drug? My guess is it probably is.

A follow-up question is do you tend to review them differently just by any chance? I don't think there are very many patients with Gaucher's disease.

DR. MOORE: That is right, there is not that many, and it is an orphan drug, however, we do not change our approach in review of the Chemistry section just because it is an orphan drug. We apply the same stringent criteria. For example, for this drug, the characterization of the cell banks in Chinese hamster ovary was extremely stringent and thorough, and the in-process controls for this very complex drug are very thorough and complete, and along with the final specifications and tests and stability, et cetera, for this drug, they were treated no different than we would treat an analogous drug that was for widespread use by patients.

DR. TAYLOR: Dr. Branch.

DR. BRANCH: Could you maybe respond to why it

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came to CDER? It stands out as being the one product that it is hard to identify as a hormone, it is a very complicated product. Is there a reason? There has to be an underlying reason why it came to you rather than going to CBER.

DR. MOORE: There is a reason. The previous drug, which is made from human placenta, made by the same company, called Ceredase, was originally in our division before the intercenter agreement, and also animal drugs are also included.

DR. CHIU: I will clarify that. Based on the intercenter agreement, it doesn't matter what kind of product, if it is derived from human source or derived from animals, they are drugs, they are not biologics.

Originally, Ceredase was derived from human placentas, therefore, it was a drug and regulated by Center for Drugs. Then, later on it changed the manufacturing process, and it become a recombinant product, so it stayed in the same place.

This happened before the intercenter agreement was signed. If you want to say in CBER, erythropoietin is a hormone, however, it is regulated in CBER, and not in CDER, although the agreement said that hormone should be in CDER, that product was regulated in CBER before the agreement was

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signed. So, once the agreement was signed, we decided not to swap, keep where it is.

DR. TAYLOR: Dr. Brazeau.

DR. BRAZEAU: I would like to address what I think could be potentially a very important scientific problem. We have heard about the characterization of purified peptide substances and how they would do that with respect to immunoassay sequence, and then look at the purity or impurity profile.

What I think needs to be done in these guidances or whenever things are developed, is that not only do you have to look at the purity and purity profile of the purified peptide, but you had better do the same thing in the final product, because these final products are going to be in different buffers, different pH's, and I am afraid if these aren't well characterized by the initial manufacturer that you will have the Premarin story time and time again, that you will have the issue of when you put this purified peptide that have an impurity and it interacts with some other vehicle, you might get something different, and then when they go to characterize it, this company, the original manufacturer will say, listen, we have got this peak, the new company doesn't have this peak, we don't know if it is active, but we are going to see the same story time and time

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again.

So, I think when you go and look at these peptides and proteins, you have to characterize, not only the purified peptide, but you had better well look at how it is going to interact in the vehicle, because most of these are going to have to be placed in some type of vehicle that may have a different type of excipients, and that is going to be a very critical question to address.

The second thing I wanted to ask Dr. Moore was, when he was talking about developing some of these guidances with the Biotechnology Technical Committee, will he follow the same procedure of having a panel of expert witnesses? It sounded like there would be some discussion back and forth between the working groups and the Technical Committee, but will these guidances also involved technical working groups?

DR. TAYLOR: Who would like to respond to the first question?

DR. NIU: The peptide, when it is a finished synthesis, there is a lot of impurity in there, some impurity, it is quite a large amount in the final purified peptide, however, because the peptide is a very long organic compound, long-chain peptide, and sometimes it is very difficult to either isolate and identify, and even though

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you have immunoassay analyzed in the mass spec, and you might be able to figure it out, however, right now in our committee, we try to decide what is the percentage of the peptide we have to characterize, and what is the percentage we don't need to characterize.

So, this is going to be determined in our working group, and into the drug product -- because this is impurity -- so we have to look very carefully in the drug substance itself, because it already formed the products, then, the impurity is already there.

So, the first document we are going to revise, that is the synthetic drug substance, that is a document. Before, we never intend to see what is the restriction of the impurity in the peptide itself, but right now we are going to address this issue.

DR. BRAZEAU: I think you are going to have to be very cautious and make sure that you do know what exactly these impurities are, because I think, as our analytical techniques get more sensitive, and our biological assays get better, we could find that these small impurities could have some activities, and then you are going to be faced with again, as I said, the Premarin story perhaps time and time again.

DR. NIU: Right now we have an issue about whether

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we should do the biological activity test, and also the toxicity test, and before they put into the market.

DR. BRAZEAU: I think you absolutely have to be able to know, when we start talking about the very similar antibiotics, what is the more critical issue, is it the activity or is it the concentration of that particular peptide and protein? I would argue that you had better make sure that the activity is exactly as you expected, that you are going to have to be very rigorous on the biological activity. I think that is going to give you some good signs in addition to the other purely physical-chemical characteristics.

DR. TAYLOR: Dr. Vestal.

DR. VESTAL: Just kind of a followup. I just wanted to ask you, in these synthetic processes that are associated with the production of some impurities that you can't get rid of, is it such that the production of the impurities is reproducible? In other words, from batch to batch, do you get the same quantity of impurities in the same profile?

DR. NIU: The most likely, if you use the same manufacturing process, that means that you use, for example, use a solid-phase synthesis, and with the same coupling reagent, the impurity profile may be the same, but if you

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change that coupling reagent, and different protectant group, such like an F mark compared with a T bar, it maybe have a different impurity profile. So, this depend upon your manufacturing process.

DR. VESTAL: Okay.

DR. BRAZEAU: I want to follow up on that, too. If you look at the purified peptide in the solid state, isn't it also important to look at it if it is going to be in a liquid state, and see how those characteristics change, because some of these proteins act differently in solid versus a liquid state.

DR. NIU: The solution-phase method and the solid-phase method, synthesis are quite different.

DR. BRAZEAU: I am talking about when you are characterizing these.

DR. NIU: Characterize, in the solution, and I think in the solid state and in the solution phase, in the solution, the impurities should be the same. There is no difference in the solid or in the solution.

DR. BRAZEAU: Would it be useful to have us do some CD on some of these proteins?

DR. NIU: Because then the short synthetic peptide, the confirmation usually is random, then, the CD probably will tell you whether that is a short peptide, have

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some kind of confirmation.

DR. BRAZEAU: I think that is critical to have because confirmation is how proteins and peptides work.

DR. NIU: Peptide may not -- because when they reach the binding through the assay or receptors, the confirmation may not be the same as your CD run for the confirmation.

DR. BRAZEAU: But can you make the assumption that if you run the CD and it has the same confirmation with the CD from time to time, that it should therefore act the same when it goes to the receptor?

DR. NIU: Yes. The CD will give you a ballpark of that confirmation, but for the small, linear peptide, the confirmation may be dominated by the random confirmation.

DR. BRAZEAU: I would just proceed with caution.

DR. NIU: Yes, I know, but you can do the CD study, but whether that is the most important character of that short peptide --

DR. BRAZEAU: Well, I am not saying you do that only, but I think you do that in addition to what you have got here. I think you need to look at that purified peptide in both a solid and in a liquid state. I think that is going to be critical.

DR. NIU: In the solid, it is very difficult to do

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the CD unless you put in them -- that is a membrane, other type of things, and it is very difficult to do the CD for this type of things.

DR. TAYLOR: There was a second issue.

DR. BRAZEAU: The second issue was a simple question. The Biotechnology Technical Committee, when they are developing these guidances, I didn't hear in the presentation if they are going to be utilizing expert committees. Will that follow the similar process to what we heard about yesterday, about using expert committees and helping to provide some recommendations for these guidances?

DR. MOORE: Our working groups, the members are carefully chosen. These are our in-house experts in these areas to develop these guidance documents. After the working group develops a document, then, it is sent to the subcommittee under the CMC CC.

The process for the Biotechnology Committee is not different than any of the other committees, such as Drug Product, Drug Substance, Packaging, et cetera.

DR. TAYLOR: Dr. Williams.

DR. ROGER WILLIAMS: We haven't discussed this internally, but I think it is a good question, but what I could imagine, as this synthetic peptides working group moves down the path, we might bring it to this committee for

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a public discussion, say, in the fall or spring depending on their timeline, and sometimes in the advisory committee, as you know, we can supplement the membership with an expert who can add some further thoughts. You know, we can talk about this as we move down the path. I think it is a good suggestion.

DR. TAYLOR: Dr. Zimmerman.

DR. ZIMMERMAN: It appears that the biotechnology products come to the Office of New Drug Chemistry for review. Does the Office of Clinical Pharmacology and Biopharm, are they involved in the review, as well?

DR. CHIU: Yes. They are involved in the evaluation of bioavailability and pharmacokinetics, pharmacodynamics.

DR. ZIMMERMAN: Is there a similar kind of office in CBER for clinical pharmacology and biopharmaceutics?

DR. CHIU: No, I don't think so. Maybe Ira can answer that better. In CBER, they have an Office of Therapeutics, which regulate most of the biotech products, but under there, I think they have a Clinical Pharmacology.

DR. BERKOWER: Actually, I don't know. I am in Vaccines, but as was mentioned, the Office of Therapeutics is trying to, in many ways, operate in a more CDER-like fashion, and they do have an Office of Clinical Trials.

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I would actually like to try and tackle something that you raised earlier, which is some of the differences between CBER and CDER. My understanding besides that there is more than history as to whether a drug goes to Biologics or not, and we tend to focus a lot more on the process, not just the final product, and we have -- I think we focus a lot on lot-to-lot, lot releasing, and the process, that the process should be managed carefully, so that the final product doesn't vary in ways that we don't actually know.

Also, lastly, we have kind of a philosophy of lot release testing, that what lot release testing does for us, besides sort of getting the definitive chemical characterization of the product, is also basically to predict failures, that we have set up a whole series of early warning signs, that if any of those are wrong, that might predict performance or lack of performance.

So, I think there is a little bit of a difference of philosophy, and I think that the result of that is, is that some products very much, very clearly should be subjected to that kind of review and regulation, and then there are some that you have been discussing here that are more or less in the gray zone, and there are others that are clearly defined chemical entities and clearly belong in drugs.

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The gray zone ones I think are the ones that people complain about. The example of things that are clearly related to process are some of the things that are very much related to the establishment of the Center for Biologics.

For example, in the area of vaccines, when there is a killed vaccine, to make absolutely certain that the process kills every last one. So, we really do focus on the process, and in the history of our center, failures of that type were really very, very important.

Another example would be in the case of a live vaccine, you can't do anything to kill the live vector, and it was grown in a cell line, and you certainly hope that the cell line wasn't growing something else alongside at the same time, and, of course, there have been examples where that happened.

So, we very much focus on the process, and we also, as I say, set up these early warning signals that perhaps something is not as it should be and that this would predict either safety problems or efficacy problems in its actual use.

So, just to sum up, it seems to me there are some products that are very CBER-like, and I would say the all-time classic is a unit of blood which has zillions of

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proteins, has the red cells that are supposed to carry oxygen, and it may have every virus known to man plus the ones we don't know. The processes are an early warning sign.

DR. ZIMMERMAN: I understand what you are talking about when you talk about vaccines and blood, and those kinds of issues, but I am more concerned about the therapeutic agents that are the products of recombinant technology, and even if the process is precisely controlled and you get your final product, it has to be evaluated in people, and I would guess that these recombinant products from a pharmacokinetics standpoint are extremely variable in humans.

The question is whether -- and I am ignorant about this -- what kind of testing or pharmacokinetics and pharmaceuticals and biopharm, and all those kinds of things, who oversees that for these kinds of products?

DR. BERKOWER: I will try to answer that. There is a Clinical Trials group that has been set up in Therapeutics to address these very questions. That is actually all I know about the answer to that part, but I would like to give an example.

In Vaccines, the pharmacokinetics and pharmacodynamics are not very well understood. How long

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does a vaccine have to stay in your muscle to elicit antibodies? Are simple concepts, relatively simple concepts, like the peak and the area under the curve, do they apply to vaccines, and is that the key thing to keep your eye on in terms of what will elicit good antibodies and good cellular immunity?

We really don't know the answer to those things. An example of the thing we don't know is what is the meaning of the lowest dose that will elicit antibodies. I couldn't tell you that today.

So, we focus on the things that we do understand. The pharmacokinetics might not be a good way to judge if two things are comparable, for example, because we don't know if that is really critical to the final result.

DR. ZIMMERMAN: But shouldn't we know that? I mean isn't that what we need to know?

DR. BERKOWER: Shouldn't we know that?

DR. ZIMMERMAN: Yes.

DR. BERKOWER: Oh, yes, we should know that.

DR. ZIMMERMAN: I will tell you my bias here, and that is that again my industry friends have told me that in CBER, there are no pharmaceutical scientists, you know, the way that I would describe myself as a pharmaceutical scientist, a pharmacokineticist, a drug metabolism type

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person, and that these kinds of issues are given short shrift over there, and there is concern with the development of therapeutic agents by recombinant technology that they are not being evaluated in the way that a pharmaceutical scientist would think that they would need to be.

Again, this is all sort of anecdotal and hearsay from my standpoint, but I am just trying to get at a good understanding of how things are handled.

DR. CHIU: I would like to clarify that. I don't think that is quite true. For example, I understood -- like TPA, which sort of characterize the biotech product, now I know that CBER has taken a very serious look at the PK/PD because during the manufacturing change of TPA, and the chain was broken, so it become a two-chain product, and then it has a different pharmaceutical kinetics profile.

For CBER actually notice of that, and then made it, went out to the company, and then took action on it because of the changes of PK/PD. A similar thing was happening to erythropoietin, a different company made a product and it has different in vivo profile, so they do look at those things.

They may not have so-called designated pharmaceutical scientists, but their reviewers do look at the PK/PD bioavailability issues.

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DR. TAYLOR: I think we have brought those issues to your attention. I think you just have to respond to them as we don't have any documentation, so I think to continue to pursue that might be -- yes, Dr. Brazeau.

DR. BRAZEAU: I would like to ask, at CBER or CDER, who is responsible for characterization of things like the adjuvants which are used in vaccines, because it is my understanding that these adjuvants can be quite varied and can certainly impact upon the effectiveness of a vaccine. So, I was wondering where that is handled and what is being done along that avenue.

DR. BERKOWER: Well, we do adjuvants in my place. A common criticism of CBER is that we have a grand total of one approved adjuvant, which is alum, and I would say, first of all, we have the accumulated wisdom of many, many years of using alum, but on the other hand, we don't -- in the sense that you were saying before, Dr. Zimmerman -- we really don't understand even the one that we have that well.

For example, some companies like to formulate the protein inside the alum, and some like to formulate it on the surface of the alum. Which is better? I really don't know. I put it on the inside of the alum myself.

I think a bigger issue, though -- I don't mean to trivialize this at all -- is in developing new adjuvants,

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how do we go about that. The approach that we have, as I understand it, is we have immunologists who are actively engaged in the field, who are very open to consider new adjuvants.

We have a big problem in vaccines. I would like to give the example of the AIDS epidemic, but there are many other diseases in this world where, if we could enhance adjuvant effects, it would make a tremendous difference, and we very much encourage development of adjuvants, and we are studying adjuvants.

At the current time, in the Center for Biologics, in the Office of Vaccines, in the division that I am in, which is called the Division of Allogeneic Products, we do have biophysicists studying the physical and chemical properties of alum and other adjuvants.

DR. BRAZEAU: I guess I might suggest that as you read the literature on nanoparticles and nanospheres, and all those different types, many of those are themselves, when a vaccine is formulated in them, seem to have some good adjuvant properties themselves, they seem to be able to stimulate, and I would think that a working group combined of both individuals from CBER and CDER looking at some of the adjuvants that are being used and being proposed in the literature would help to provide you at least with what

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might be coming down the pike, because I really do think that alum certainly has been our old standard, but there are more out there that are seeming to become useful.

These are people from the biotech companies that know a lot about that.

DR. BERKOWER: We are very interested in having new adjuvants being developed, to be developed, and --

DR. BRAZEAU: Well, these aren't adjuvants, these are the dosage forms themselves. These are when we put some vaccines in, my reading is putting some vaccines in nanospheres, nanospheres themselves, or nanoparticles, actually provide the -- the dosage form actually provides the adjuvant, so if you start dealing with dosage form, then, you have got a much more complex system here.

DR. TAYLOR: Dr. Williams.

DR. ROGER WILLIAMS: I think in fairness to Dr. Berkower and probably so his center management doesn't have a heart attack when they see this transcript of this meeting, the reality is CDER has nothing to do with vaccines, and I actually am delighted, for one, to say that, because they are so complicated, they kind of violate my notions of what a small molecule should be doing.

I think you got a sense from Dr. Berkower that sometimes the messier these things are, the better they are

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in terms of a product. But I would like to perhaps bring this committee to I think issues that we will be struggling with in the future, and I think Dr. Brazeau addressed some of them.

I think we are struggling with the issue, as always, of sameness. One of the questions connected with that is something we call characterization, can you adequately characterize these drugs, or is there something about them, so that the process controls the product.

Now, that is a very important branch point in my mind, because if you say the process controls the product, first of all, I think you forestall generic substitution, you make it very difficult unless that process becomes widely known, which is very unlikely. It obviously would be a closely held secret by the innovator.

Second of all, you make it very difficult, then, for the innovator to change anything, you know, and I don't know if it is apocryphal, but somebody told me once that Dr. Kessler got very angry because somebody said in CBER that if they wanted to move a refrigerator, they had to file a supplement. I don't know if that is true, but it was some of those statements that led to the REGO initiative and the kind of push from on high in our agency to bring CDER and CBER closer together in terms of what we do.

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So, I think that issue of characterization versus process is a critical one, and I have seen -- a lot of my understanding is naive compared to these experts -- but I have seen movement over the last several years with improved analytical methodology and better techniques that for many of these things you can adequately characterize them, and I think there have been workshops to that effect, et cetera, et cetera.

So, to me that is a terrific hurdle, and if nobody minds -- I forbade myself the use of the P word, the Premarin word -- but one of the issues with Premarin is could it be adequately characterized, and I think our feeling is -- and please correct me -- that maybe it not now adequately characterized, but it could be adequately characterized.

DR. CHIU: It would take a long time to characterize every component in Premarin, because there is just so many of them. However, I think Dr. Woodcock's memorandum did not say it must be characterized. She said if the composition is comparable, if the generic company make their product from the natural source, if the composition is comparable, then it could be considered the same, but the composition doesn't mean you have to identify every component, you have to know the structure, give it an

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name. You have similar profiles.

DR. ROGER WILLIAMS: So, if I can continue, I will be done in just a second. That issue we still have to struggle with, with Premarin, and I think what Dr. Chiu was alluding to was the possibility that you could compare chromatograms as a way of assuring comparability without actually identifying each little peak on the chromatogram.

That is a very interesting thought. I don't think we do that too often in CDER. We tend to say here is the active moiety which can be completely characterized.

Once you get past that branch point of, say, process versus characterization, if you will, then, I would say you get into the issue of what are the active ingredients versus what are the impurities.

Again, Dr. Brazeau brought that to our attention. I think that is a very critical question. Now, I would argue that the new drug process in CDER typically identifies the active moiety and the active ingredient. I mean to me that is what in some ways the new drug process is all about.

The idea then via the application and the USP monograph, you control the quality of that active ingredient and try to minimize impurities. I think we all think impurities are things you don't want to be there, and the thought of putting a lower bound on an impurity kind of

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irritates me, I have to say, because it sort of says it has to be there.

Well, if it has to be there, is it contributing to the activity? These are all very deep, difficult questions. Now, I would argue -- and you saw from the presentation this morning that we are going to try to tackle these issues by drug substance class in the realm of biotechnology, starting with synthetic peptides and moving down the list that you saw.

Of course, as we move down the list, it is going to become more and more difficult. Getting back to what Dr. Branch said, if this committee wants to have what it does over the next several years, I think these discussions will come up time and again.

I will just conclude by saying this. It would all be wonderful if it were just science, but our regulatory structure creates via Hatch-Waxman and the Orphan Drug Act the possibility of three-, five- and seven-year exclusivity, which immediately intrudes the challenge, and I must even say the hysteria, of economic considerations into it, which I think tend to cloud the issues and make it much more difficult to come to a science judgment.

DR. TAYLOR: Dr. Branch.

DR. BRANCH: I think you very nicely posed an

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issue. The question I would have is given that the scientific base is changing, and changing rapidly, and that you have taken the scientific principle as being underpinning the regulatory authority, how do you actually keep the science base internally running contemporally? The difficulty comes in, for example, of the specificity of the actual moiety versus its biological activity.

Vaccines isn't in your area, but I thought it was an excellent illustration of some of the complexities that have taken place when you get to more complicated molecules where you are not going to have a pure, single entity that is being put into somebody.

At the end of the day, it is a biological response that you are trying to elicit from a patient, so how does the Agency manage to keep itself contemporary with science is my question.

DR. ROGER WILLIAMS: I would encourage these fellows, too, but I might say some of it -- I think it is multifactorial -- some of it is here, it happens in this kind of advisory committee meeting. Some of it is via the working groups and the technical committees to get key experts from both centers together, and I am delighted to see the way the Synthetic Peptides Working Group has formed itself, because there is a real synergism of thinking and

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understanding.

I think that collaborative enterprises that I keep talking about are a way of doing that, and, of course, there are many other ways, professional societies, public workshops. But it is a key question, and I would argue that if you -- you know, in my mind, the basic thing to do is kind of figure out what is your question that you are trying to answer in any given circumstance, and then let the science address that question as best it can.

Now, that is why I positioned this whole debate in terms of pharmaceutical equivalence, and it is very similar to the debate you heard for the small molecule from Dr. Srinivasachar and Dr. Duffy and Dr. Byrn. It conceptually isn't different. You are trying to say do you have the same molecule after a set of changes.

Of course, the science challenge becomes just much more cumbersome when you are dealing with a biotechnology product. If I can just take one more second, I might say we rarely say that for a small molecule you would have to do a clinical study to say that it still has the same activity. I mean that is one of the triumphs of the 20th century, if you will, that you can completely characterize this small molecule.

When you get to pharmaceutical equivalence,

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though, and these more complex molecules, you do begin to ask questions like does it have the same animal PK/PD, the same human PK/PD, the same clinical safety and efficacy, and it has been fascinating to me that those same approaches you use to ask the bioequivalence question for the drug product, you can use to ask the pharmaceutical equivalence question for the drug substance, and I don't want to scare anybody, but I think the question of metrics and statistics comes in here, and I even raise the dread word individual equivalence because in some ways I think this is a switchability question, not for the drug product, but for the drug substance.

I watched Marie's face turn pale when I said that, but I think it might be a great debating point for the committee at some point in time.

DR. TAYLOR: Let me just add, as I listen to this discussion, of making sure -- and I am sure the Agency considers this, and I heard this in your response, Dr. Williams -- of some balance between, as we get out on that biotechnology limb, of characterization and active product versus getting product to people who need it, and I think we have to be aware of that, and as pharmaceutical scientists or pharmacologists in academia, we may want to go to the nth degree to prove our point in terms of what is the active

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ingredient, but I think there is a practical side of it, as well, in terms of not only cost, but continued development in the industry to make sure we have products like that.

So, I wouldn't want to rush to a lot of reductionist kind of work trying to get to the active product in some of these new products. That will come as we evolve, but I think the practical side has to be considered, getting product to people who need it.

DR. WALKES: I think that is true, but I think that we need to be sure that we are providing safe products.

DR. TAYLOR: I am not saying it is not safe, but I mean like the Premarin issue, if we had to try to characterize Premarin, Premarin has been used for how long now, 30, 40 years, it is safe.

DR. WALKES: Well, that is true.

DR. TAYLOR: We may never know what the active ingredients of that is.

DR. WALKES: But during the discussion this morning, we are talking about entities that we can't put a finger on and characterize specifically. Maybe the chromatographic studies would help, because that may show some similarities, but as a clinician, you want to know that if you give something, you have a certain amount of surety that you are going to get the response that you are trying to

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get.

So, what I am hearing is that is going to be very variable, and we need to know that. We need to know that as we use the product, we may not get -- the hepatitis B vaccination series, I mean some people don't develop antibodies, well, now I know why, because we really don't know how much it takes for that to happen in everybody.

DR. TAYLOR: I am not suggesting that safety is compromised. I am just suggesting that, as technology develops, that we look at the practical side of why we are here, which is to provide safe, effective drugs.

DR. GONZALEZ: I would like to raise a question to the Agency and to Dr. Williams, because it takes off on what Dr. Branch mentioned, about scientists and I guess what we are hearing for the past two days, the growth in the technological development, and that has to do with the macromolecules. There is companies in Europe, I know of one developing oral vaccine, oral insulins, oral calcitonin preparations, and when that comes abroad for us in this country to begin to evaluate, how is the Agency going to look at these macromolecule formulations, are we preparing ahead of time to be proactive rather than reactive in the challenge when someone tries to market an oral vaccine against pneumococcus or H. flu, and we have to compare that

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to a standard which we have in this country, but it is parenteral.

DR. ROGER WILLIAMS: I really can't comment on vaccines.

DR. GONZALEZ: Let me try, then, oral insulin or oral calcitonin preparations, which are being developed. Right now there are two studies ongoing with oral calcitonin for osteoporosis, and not in this country that I was aware of, I am aware of the studies ongoing in Europe.

DR. CHIU: Let me try because we did have an example in DDVAP, have vasopressin, which was an injectable drug, and a few years ago we had oral tablets, so the Agency does have scientists to have knowledge to evaluate different formulations, and then during the IND stages, the reviewers have close contact with scientists in academic and scientists in industry, and to evaluate the development of the products, not only safety, clinical efficacy studies, also the development of the pharmaceuticals.

Actually, in the Agency there are a number of dosage form of insulin being tried, nasal form, and solid product of nasal form, and transdermal patches, electrophoresis, all kinds of dosages form are being tried, so we do have interaction with outside experts and that you gain from them, and we think the two have a proper

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evaluation, and gets a final approval if it's wanted.

DR. BERKOWER: And, of course, with regard to vaccines, the various mucosal surfaces on our body are important portals of entry for a number of organisms, and it is a common belief that secretory IgA is an important protective barrier at those surfaces.

It is also believed or it is also now known that if you immunize in one area and achieve IgA, that actually there is a circulation going on in the body, so that IgA will be made on a number of surfaces.

We, at CBER, have an active mucosal immunity program, and we also have an active research going on in enterics, so, for example, that would cover salmonella-based vaccines.

DR. BRAZEAU: Dr. Berkower, I don't think -- you know, if we sound like we have been -- we haven't been going after you, but I think what I am hearing from this committee is that I think we would recommend to your boss something that you need to get some more people with pharmaceuticals in your vaccine, people with those kind of training, that can do that.

There are graduate students that are being trained in biotech that have a pharmaceuticals background, and I think we are just trying to make your life a little bit easier.

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Maybe recommending to your superiors that you need to get these kind of people on your team as we get closer, as we deal with some of these vaccine issues.

DR. BERKOWER: I would concur in that.

DR. TAYLOR: Dr. Williams.

DR. ROGER WILLIAMS: Coming back to I think some points of Dr. Walkes, I think that is a key goal throughout this entire discussion, which is to make the tests appropriate to the level of change. I mean we can all imagine that we could bog the whole process down, and it is your point, too, Dr. Taylor, that for every change I could say, well, let's do a bioequivalence study. Well, that would be ridiculous, you know, we understand some things are minor and don't need that.

I would argue that the SUPAC documents are designed to do that. You know, here is this much change, well, you have got to do that much testing. But you heard, and I heard, too, for the first time, that there is a slightly different paradigm emerging in the BACPAC, which is that the results of the tests determine the filing requirement, and I might say one of the nice things of me being able to sit here and listen to this is I get to find out some of these new approaches, but I think that is an interesting way of thinking about it, that the result

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dictates the level of filing. I think I heard that, right?

DR. TAYLOR: Yes. I think the BACPAC discussion, that is a very innovative way to approach changes in manufacturing.

I had a couple of questions that will be quick, because we are running out of time, and the question is what happens when you change a manufacturing process where you actually change the impurity profile, so that the impurity percentage may remain the same, but now you have got a different impurity, how do you handle that. I didn't see a way to do that in the algorithm.

The other thing is when would you inspect a manufacturing site where a change had been made?

DR. SRINIVASACHAR: To answer your first question, whenever you change a synthetic process, I think it is almost a given that you are going to get a new impurity because when you change a process, you could change solvents even if you use the same basic synthetic scheme and the same basic reactions. Usually, a solvent change can occur in any of the steps, so you are going to have a different impurity, and this is a new impurity.

As I mentioned in my talk, one of the ways we are considering handling this is through the threshold levels that are given in the ICH guidances both for impurities and

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new drug substances, as well as for residue of solvents, and I think these threshold levels in the ICH guidance would be a good starting point to handle new impurities that may arise from a different process.

DR. BYRN: I might add to that companies a lot of times will, if they are too high an impurity, they will reject that change, and, in fact, many companies are using, not 0.1, but 0.01 percent, many of the big companies, so what will happen a lot of times is they will try to get a new route or a change, and if they see too high an impurity profile, and they can't eliminate that, they will just say, well, we are not going to make that change.

On the other hand, there are cases where they may have to go all the way to the point of qualifying a new impurity, where you get a higher impurity. You might have to actually do a toxicity test on that impurity.

Generally, that is avoided I think, but all those are possible, but I think most often chemists would keep trying to find a way that didn't introduce very high levels of new impurities.

DR. SRINIVASACHAR: I would just add that the ICH guidance also goes into the qualification of impurities, so the industry has two options here. One is to purify the drug substance, so that the new impurity level is well below

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the threshold, but if for some reason this is not possible, then, the ICH has a decision tree approach that can be used as a guidance for qualification, and basically, again, this decision tree approach, in the very final, in the worst case scenario, this would involve in vitro or in vivo testing of the impurity for safety.

DR. TAYLOR: Dr. Williams.

DR. ROGER WILLIAMS: Just a quick comment and then maybe a request for Dr. Berkower.

It is of interest to me, and it may be of interest to the committee, as well, we have different levels of concern about the products that are available in the marketplace in this country, and it is just a fascinating point to me. A lot of what you hear happening now relates to control of prescription drug products, and as you can see, I think there is tremendous attention and focus in the Agency and in the industry to control impurities and define active ingredients.

When you go to the OTC world, some of which are given in very high doses, those are controlled by OTC monographs, and the monographs, as specified in USP, are frequently old. Now, if you look at those monographs and wonder what is going on, it is very different than what is being talked about here.

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Then, if I might go to the final thing, when you look at the dietary supplements and go in your health food store, and you talk about bee pollen and shark cartilage, and you start to wonder what is in there, I think you see the varying level of concern that somehow exists in this society.

The other thing I think it is an interesting story, and maybe I would ask Dr. Berkower, could you just say a few words about these new vaccines. There really was significant advance in terms of safety. I mean there is a story there that I think is a powerful story. You mentioned it to me. Do you know what I am talking about?

DR. BERKOWER: Give me another hint.

DR. ROGER WILLIAMS: The new vaccines for kids and how they are safer and better, and there has been an advance there.

DR. BERKOWER: I see. I did say something to that effect, yes.

DR. ROGER WILLIAMS: I am sorry to put you on the spot like this.

DR. BERKOWER: Actually, I just gave my definition of a good vaccine, it is as simple as that. One of the nicest things to come out of CBER research in the past decade was the Hemophilus influenza B vaccine. This is a

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conjugate and there are I believe four different ways of making the conjugate, but it is quite similar to the peptide protein conjugates that I showed. The only difference is that instead of a peptide being conjugated to a protein, it is a sugar, either an oligosaccharide corresponding to a bacterial outer cell wall, polysaccharide or the polysaccharide itself from the bacteria that are conjugated to a protein.

What was gained in this way was that the T cell response to the protein could then focus on and help the B cell response the polysaccharide, so the antibody response was better, stronger, and it also occurred in children at a much younger age.

It turns out that in the case of Hemophilus influenza, you have immunity from your mother at birth, it wanes by the age of six months, and it is the children from six months on, up to two years, who are then at risk of getting seriously ill from Hemophilus influenza. It can cause meningitis and death, for example.

Well, since the vaccine has come on the market, the children who got vaccinated are protected, but what is really remarkable is that even the children who are not vaccinated have had a decline in the rate of disease because they are surrounded by children who are immune, and so the

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effect of what we call herd immunity is actually protecting the children who are immunized, as well as even having an effect on the children who are not immunized. That is my own personal now view of a definition of a really good vaccine.

DR. TAYLOR: With that, then, I would like to close the morning session and we are running a little bit behind, but we will reconvene at 10:30 as scheduled.

[Recess.]

DR. TAYLOR: The remainder of the morning session will focus on the pharmacology/toxicology topics.

The first speaker is Dr. Frank Sistare.

**Pharmacology/Toxicology Topics**

**Analysis of the TB.AC Transgenic Mouse Model**

**for Carcinogenicity Evaluation**

DR. SISTARE: Good morning.

[Slide.]

Yesterday, my task was four minutes to give you an overview of the Division of Applied Pharmacology Research. You may remember this beautiful slide I showed up there.

We have four teams in our division. What we are going to do this morning is go in a little more depth into two of the teams: the carcinogenesis and toxicology team,

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and then after my presentation, Donna Volpe will present some exciting work in the preclinical/chemotherapeutic evaluation team.

What we are doing is a little bit of an experiment. We are going to go into a little more detail, actually present some data into an example of some projects that we have ongoing. So, I would like your feedback, maybe during the discussion period, and see if this is kind of the thing you want to see more of or, you know, let's stay away from details, let's get more into generalities.

[Slide.]

What I am going to talk to you about is some preliminary data that we have. I will stress that. We have one study that is complete and we have one that is ongoing, but the data are clear in terms of some of the results you will see.

It is a regulatory analysis of the TG.AC transgenic mouse model that has been proposed for carcinogenicity evaluation.

[Slide.]

As I mentioned yesterday, there is an ICH guidance document S1B that is entitled, "Testing for the Carcinogenicity of Pharmaceuticals," which has been signed by the FDA, European Union, Japan's Ministry of Health and

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Welfare, and the various respective pharmaceutical trade organizations of those regions.

That document allows the use of an alternative short- or intermediate term assay supplement, one standard two-year rodent assay without compromising human safety. As you may all know, the standard paradigm is to use mice and rats for two years, and this is saying now in place of, for example, the mouse, you can stay with it two years with the rat, but in place of the two-year mouse you can go with one of these alternatives.

[Slide.]

The project I am going to tell you about today is a coordinated effort with the NIEHS and a consortium of pharmaceutical companies coordinated with International Life Sciences Institute to assess the strengths and limitations of the TG.AC transgenic mouse model for improving the predicted value and decreasing the burden of the currently used two-year rodent bioassay for predicting human carcinogenicity.

Of the various models that the ILSI organization is looking at, the way they have organized themselves, they have set up studies to look at TG.AC, the P53, the TG-RasH2, and the newborn mouse are the ones that they are focusing on.

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Of those models, there is a lot of controversy over the use of the TG.AC. Some view it as very, very promising, others as maybe not specific enough. They use the term "too sensitive." So we felt, of the models, this is one that we probably should start looking at first.

I want to stress that the studies that we are doing is an evaluation, it is not a validation study, and none of these models have been FDA approved or anything like that.

[Slide.]

What is the TG.AC mouse model? This is a model that was developed by Aya and Phil Leder.

What it consists of is the mouse zeta globin promotor that has been linked to the v-Ha-ras oncogene with an SV40 Poly A termination site.

This transgene was injected into several mice, and they came up with one strain where the ras gene was expressed, several of the other mice that they came up with, it was not expressed, and the particular strain is AC, TG.AC mouse.

Now, the mouse model that has evolved from that, and it was picked up by Ray Tenant's group done at the NIHS, is a skin paint model for predicting carcinogenicity. The compound in question is put into a solvent, either acetone

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or ethanol, painted on the back of the mice, and the endpoint is just a measurement of papillomas.

It is a very simple model, not technically difficult to perform. Like I say, in Ray Tenant's group, there has been tremendous concordance between the various compounds that he has looked at, known carcinogens indeed induced papillomas, things that are not considered carcinogens or tumor promoters do not, so there is a lot of excitement in the pharmaceutical industry could this be a nice assay.

I will say that the time course for these kind of events to happen is usually within seven to 10 weeks you start to see the papilloma, sometimes even earlier, and by 20 weeks you know what you have, you know what you are dealing with. You don't have to do histopath, you don't have to take the animal apart, send it out for analysis, so the promise was exciting.

[Slide.]

To begin, we set goals to test sensitivity, test specificity, and to explore various issues relating to the dose route and exposure. I will backtrack a little bit and say that of the compounds that Ray Tenant's group tested, very few were pharmaceuticals, they were mostly NTP test compounds, pesticides, known carcinogens, these kinds of

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nasty chemicals, but in terms of pharmaceuticals, very few were tested. So, we wanted to expand and start to begin the process of looking at pharmaceuticals.

We chose to test sensitivity, the ability of this model to respond to a known pharmaceutical carcinogen. We chose three compounds -- and when I say "carcinogen," that term is based on the rodent bioassay primarily -- but the first compound that we chose is cyclophosphamide, a rodent carcinogen, it is actually a PRO carcinogen, has to be metabolized to the mustard, and the mustard, the phosphoramidate mustard is known to be the carcinogenic moiety.

It has also been shown from epidemiology studies to result in secondary I believe leukemias in humans, as well, so it is a known human carcinogen. It is one of the few compounds that is a known human carcinogen, as well.

Another compound we chose to look at was phenolphthalein. Phenolphthalein has been shown in two-year bioassays to result in both mouse and rat tumors. A third one is tamoxifen. Tamoxifen in mice and rats is tumorigenic. In rats, it promotes liver tumors and has been shown to form covalent adducts, as well, in at least the rat model. In the mouse, most of the tumors were of endocrine origin.

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Testing specificity was a more difficult question. You have 300 to 400 or probably even more pharmaceuticals which have gone through the two-year bioassay, and there is no carcinogenesis. How do you begin the selection of compounds to choose from those and to test this question of specificity, the question of faith that a noncarcinogen will not induce a papilloma in this model.

We chose chlorpheniramine. Why? It is a safe compound, it has been used widely. It is over-the-counter, antihistamine. There was actually a report in a paper that showed, however, that in the 3T3 Balb.C model, that there was a weak ability to cause transformation in that assay. If, indeed, this model is so nonspecific that something that weak would show up, we ought to know about it pretty soon, so we chose chlorpheniramine to look at.

Now, the first study we did is a straight skin paint study. The second study that we designed was to explore the possibility that the model could be expanded to both skin paint and oral administration, and the reason we did that was because of some recent data that Ray Tenant had shown that benzene can cause granulocytic leukemias after topical administration, so enough was getting in to cause the systemic carcinogenic event.

So, we asked the question if we administered

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tamoxifen and skin paint, will we get papillomas, if we administer it orally, will we see this granulocytic leukemia with that, as well, and then that would also, like I say, expand the practical use of this model.

Like I said before, the questions of metabolic activation, painting something on the skin, will something like cyclophosphamide, which means metabolic activation, will we see that after a skin paint.

Also, questions relating to solvents came to the forefront, and I will get into a little bit more of that.

[Slide.]

To put it in historical framework in terms of our starting point, where do we begin, and also to point out the stuff that Ray Tenant had published was with the homozygous, both alleles expressing the transgene.

As the ILSI group decided on how to plan their attack, the decision was made by ILSI to go with the hemizygous mouse model, and our studies were done with the hemizygous mouse.

The does. How do you chose the dose? The way Ray Tenant did it was again we are using compounds for which we have two-year bioassay data, and the way they did that was look at the dose that the animals were exposed to during the week, take that dose and administer the same weekly dose to

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these animals, and these animals, like I say, are skin painted, they are getting it over two or three applications. Those are really high concentrations of the drug being applied to the backs of these skins.

Ethanol and acetone, as I say, was promoted by Ray as acceptable vehicles. Also, a nice feature of this model is you have a positive control group, and for the positive control, tetradecanoyl-phorbol-acetate, TPA, also called PMA, phorbol-12-myristate-13-acetate has so many different names, but anyway, when I say TPA, I am not talking about tissue plasminogen activator here. I am talking about this phorbol ester. The positive control specified at the beginning of the ILSI consortium group was 1.25 micrograms twice a week.

Here comes the data.

[Slide.]

The data didn't turn out quite as we expected it. In our first study, after seven, eight nine, ten weeks of skin paint with a positive control, 1.25 mcg of TPA twice a week, what we expected to see was a curve kind of like this. That is the kind of stuff that had been reported in the literature.

Instead, we were getting nothing. So, about week 13 we made the decision, said okay, let's split up the

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groups, and at week 13 we gave half of the animals TPA 10 mcg twice a week, and we kept half of them at the same dose of 1.25 mcg twice a week.

Now, the little blip that you are seeing here, you see the data expressed as average numbers of papillomas per mouse. What we got here is we got like one animal, one male and one female that expressed like 15 papillomas, but all the other animals in that group did not express any papillomas, and that, as it turned out, was also in the 1.25 mcg twice a week. None of the animals switched to 10 mcg twice a week got any papillomas here.

Cyclophosphamide we got nothing, phenolphthalein we got nothing, and chlorpheniramine we got no papillomas for the entire -- we actually dosed for 26 weeks -- we went longer.

[Slide.]

Now, one of the points that was brought up to us was we were using PMA and ethanol. The reason we did that was because all the other compounds we used were soluble in ethanol, and were not soluble in acetone at the concentrations we needed to apply. We wanted to use one solvent. Ray brought to our attention that he had always used TPA in acetone, didn't use TPA in ethanol.

We went into the literature. We found some old

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data by Tom Slaga using the Sencar mouse in which he showed that TPA and ethanol was about five times less sensitive than TPA and acetone, he needed five times more to get the same papilloma response in that animal.

So, Study 2, we modified our original plan and we asked the question about solvent, is there an effect of solvent, indeed, in this model, with respect to TPA. Like I say, Study 2 was also designed to look at oral versus topical administration of tamoxifen.

So, we said, okay, when we look at the effect of solvent, let's look not only the positive control, but let's look at the test compound. So, we have tamoxifen citrate, which is in ethanol, and we have tamoxifen base in acetone.

You can't really see much here. I am going to show you another slide you begin to see something over here when you express it, not as average numbers of papillomas per mouse, but number of mice with papillomas, with any papillomas.

[Slide.]

But if you look at this, TPA and ethanol, we went with 1.25 mcg twice a week, and we went with 6.25 mcg twice a week, again because of the Slaga data showing a fivefold difference in sensitivity. TPA/ethanol - skin paint 6.25 females/males versus acetone females/males, not a heck of a

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lot of difference here.

1.25 mcg twice a week in ethanol versus acetone, again, very, very little response in the second study, as well.

In conversations with at least one other site which was doing the study at the exact same time, actually, they were like a week ahead of us doing the study, and they were using 1.25 mcg twice a week, they were also not getting responses out to week 13 or 14 at that time, as well. So, this has been produced in at least one other site. I will not mention where that was done at this point.

[Slide.]

So, to express the data a little bit differently, you look at percent of animals in your group with papillomas, you can see we are starting to get a little bit here with the free base and acetone.

Here is the same data with TPA with ethanol and acetone.

Now, what we have is about 30 percent of the animals responding in terms of the males, and the females about 70 percent of the animals are responding. Over here, across the board with acetone we are getting about 30 to 40 percent of the animals are responding in the high dose group. In the low dose group you get a papilloma, it goes

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away, you get a papilloma, so we are starting to get a little bit of response there, and a few of the animals with a very, very low papilloma load.

[Slide.]

If you look at the data a little more closely, and if you look at the individual animals in the female group, of the 8 animals in this group, 5 are responding and 3 no responses. We stopped counting papillomas after about 30, 32 papillomas, in fact, some of these animals have 40, 50 papillomas, but in the same group of animals being treated with this high dose of TPA, there are animals which are getting nothing.

[Slide.]

If you look at males, here is that response that we were looking for, that five, six, seven, eight-week climb. In the males we get two with a full papilloma burden, one with partial, and we got seven out of the ten animals we are getting no response at all. Again, this is very different from the kind of data that we were seeing in the literature where you are getting 70 to 90 to 100 percent of the animals all responding at least with the homozygous animals.

The first question we asked is, gee, are we getting in our nonresponders and responding animals, is

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there any difference in terms of this transgene being present, we did southern blot, our probe to the SB40 Poly A, so we are not going to pick up any endogenous ras or any endogenous mouse zeta globin, and the only thing that should light up on the southern blot is the transgene.

[Slide.]

If you look, this is just the ethidium bromide stain just showing pretty good equal staining across the board in this particular blot. I have another blot in your handouts which there was one lane which was underloaded, and you could kind of see that in the southern, as well, but as you see here, we got responders, nonresponders, nonresponders, nonresponders from Study 1. We got responders and nonresponders in Study 2. It doesn't make any difference, the transgene is there. It is there, so it is not a question of it not being there. For some reason it is just not being expressed as well in some of these nonresponders.

[Slide.]

Another question that we asked is as we move from these chemical carcinogens to the pharmaceuticals, one thing we found was -- and the reason we used ethanol -- was because we couldn't get these things into acetone. Solubility characteristics are going to be very different

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with pharmaceuticals which tend to be more water soluble as opposed to these carcinogenic chemicals which tended to be more lipid soluble.

So, we needed to start to get a handle on how can we be sure that when we paint the pharmaceuticals on the skin, it is actually getting to the site of origin or the site where the papilloma is expressed, and it is expressed in the follicular cell of the skin. That -- and I should have said upfront -- is really a mystery as to why this particular cell type expresses this.

The zeta globin gene is a very tissue-specific and developmentally-specific promotor, why is it expressed in the follicular cell of the skin remains a mystery, but there apparently are some transcription factors which are apparently present there to allow this to be expressed.

So, to ask the question, you know, how can we be sure there is getting penetration down to the follicular layer with cyclophosphamide, we looked at, at least if we are getting it into the blood, it is getting through the skin, so we just asked the question can we measure it in the blood, and indeed, we can. Estimates are something like 1 percent is actually getting across, is a very low percent, and again that is something we have to think out. The dose of cyclophosphamide we used was perhaps too low, was based

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on the two-year bioassay data.

If you are dealing with something that is very lipid-soluble, you can see why you might want to stop at that dose, but for something that is not going to get across the skin, you can probably push the dose up 10, 100-fold. We have to reexamine that whole issue.

[Slide.]

Chlorpheniramine, from the previous slide the concentrations that were reached in the blood were about 150 nanograms/ml. Here, we are using 10 times as much chlorpheniramine. We are getting around 3 to 4 mcg/ml, 20 to 40-fold more when we use 10 times more drug, roughly proportional. So we are able to measure chlorpheniramine getting across.

With phenolphthalein, however, I don't have a slide showing this because we couldn't find it. It is down here below 500 nanograms/ml, below the limit of sensitivity in our analytical method. The dose that we were applying to the skin was twice as high with chlorpheniramine.

So that raises an issue about when you apply something to the skin, whether or not it will penetrate and get to the follicular layer is an issue that has to be resolved. With phenolphthalein, we have been able to demonstrate it just doesn't get across into the bloodstream.

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[Slide.]

So, what are the lessons we have learned? As we progress with this model, we are going to stay with the two-dose positive control group. It is nice to know whether or not we are getting a shift in sensitivity. However, that 1.25 mcg is too low, and 6.25 mcg is unnecessarily high.

10 mcg TPA at that age of 20 weeks was not papillomagenic. Acetone and ethanol appear to be interchangeable with TPA. I told you about the phenolphthalein. This question of phenotypic segregation, responders and nonresponders raises this whole question about animal variability and what kind of quality control parameters need to be set up as we move to the use of this model.

[Slide.]

We talked about that, penetrability, and it raises that whole question is cyclophosphamide not papillomagenic in this model.

[Slide.]

That is a question that we have to revisit, and a really important question. If a human carcinogen is not papillomagenic, but the whole question may be dose, it may be the quality control of the animals. The whole specificity issue is still wide open, and I will just mention that we

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have a reporter gene rapid screening strategy to look at that more carefully.

I will stop here.

Next, presenting will be Donna Volpe. What I have talked about here, questions relating to carcinogenesis, questions that the pharmaceutical industry deals with as things are moving into the IND, into the clinical phase of things. They don't have to be done prior to the clinical trials.

Donna is going to be talking about some more which really interface much earlier on in terms of decisionmaking.

### **Prediction of Myelotoxicity with In Vitro**

#### **Hematopoietic Clonal Assays**

DR. VOLPE: Good morning.

[Slide.]

I am going to talk about, as Frank said, something that occurs in the preclinical phase of drug development. I would like to give you a little overview of myelotoxicity in the assays we use and then give you two projects that we have worked on or are currently in progress.

[Slide.]

The goal of preclinical drug development is to predict a drug's efficacy and its safety in how it will behave in clinical trials. Historically, animal models have

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been used to predict human toxicity, but increasingly we are seeing human tissues and cells being used to predict human toxicity.

One such thing is to use bone marrow cells to predict toxicity to the hematopoietic system.

[Slide.]

We are able to use human tissues to predict myelotoxicity, and in our hematology program we are seeking to develop and evaluate optimal models in vitro for the prediction of myelotoxicity that will aid in the acceleration of clinical trial design whether it be determining a starting dose or determining an escalation scheme, and this is particularly true with the anticancer drugs and antiviral drugs. This is where you see the myelotoxicity most often.

[Slide.]

Our program seeks to build bridges between the preclinical and the clinical drug development, and this can be done by both predicting the clinical drug safety from cellular endpoints -- meaning the in vitro to in vivo extrapolation -- also by assessing the relevancy of animal models to the human situation in an interspecies extrapolation.

[Slide.]

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Myelotoxicity is the most common dose-limiting factor in cancer chemotherapy. It reduces the amount of drug that can be given to a patient, either the amount that is given or the number of cycles that the patient can go through with the drug therapy, and it can increase the time between cycles. It can result in longer times between the cycles, how much drug, and you can get hemorrhaging and the potential for neutropenic fever.

Now, the severity of the myelotoxicity is determined by two factors, one being the drug characteristics, the dose of the drug, how it is cleared, how fast it is cleared, and its mechanism of action.

The second factor is the patient themselves, how old is the patient, what is their general health, what is their bone marrow reserve, had they been treated before with other cancer drugs, have they undergone radiotherapy. If they have a low bone marrow reserve, they are going to be more susceptible to myelotoxicity.

Lastly, the onset of myelotoxicity is determined by the cellular kinetics in the bone marrow and by the life span of the peripheral blood cells.

[Slide.]

The hematopoietic clonal assays provide us with a well-defined system to analyze the toxic potential of drugs

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to both human and animal cells. We use cytokines to stimulate the progenitor cells to both proliferate and differentiate, and a number of results in colonies that we get in our assay is proportional to the number of viable progenitors in that population.

The degree of colony inhibition resulting from in vivo or in vitro drug exposure is then used to predict and evaluate the toxicity of the drugs.

[Slide.]

Different from the slide that you have in your folder, I have more of a cartoon schematic slide. This is to depict both an in vivo exposure of the drug to the bone marrow cells or an in vitro exposure.

In preclinical development, we can have a rodent, a mouse or a rat, exposed to the drug or a dog, most likely a beagle dog. After the exposure of the animal to the drug, say, a specific time period, it could be a single exposure or multiple exposure, you can isolate the bone marrow cells and then mix them with our culture media.

In the case where we have a semisolid matrix which can be a methyl cellulose, an agarose, or a fibrin clot, also, in this mixture will be a fetal bovine serum or a serum substitute, and cytokines to stimulate the formulation of colonies. This will be then plated into a 35-millimeter

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dish or a 24-well plate, and after a requisite incubation time, you will be able to count the number of colonies, and you would look at colony formation after an animal has been exposed to dose X, Y, and Z, and then see the results in number of colonies.

Alternatively, we can expose the bone marrow cells in vitro to the drugs. In this case, we can also look at rat, dog, and human cells, isolate the normal bone marrow cells, and expose the cells in a test tube to the drugs for a time period. The time period may vary from one hour to 72 hours.

After the drug exposure is complete, we can wash away the drug, mix the cells with a culture medium, such as agarose, the cytokines, the serum, and then plate them again in the assay dishes, and at the end of the time period of the incubation, count the number of colonies. We can look at colony formation versus concentration.

The advantage of these assays is you can combine drugs, look at two different drugs together or look at drugs that are exposed one after the other.

[Slide.]

The question that we have to ask is are these hematopoietic assays useful to us in the preclinical drug development, can they predict clinical myelosuppression, and

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we have shown with a series of drugs that we can see a qualitative prediction of myelotoxicity. If the drug is toxic in our assay systems at a certain concentration, it will most likely be toxic to the people.

Can we predict relative toxicity? Well, this would be important if you have a series of drugs that you want to screen and pick the drug that is least toxic, and, yes, we have shown this with a series of dideoxy nucleoside antiviral agents from AZT, DDI, DDC, D4T carbovir.

If you take the rank order of the toxicity of these drugs in vitro and look at the rank order of the toxicity of the drugs clinically, you see a concordance.

Can the assays predict toxicity to a specific cell lineage, such as neutrophils, platelets, or red blood cells? We have shown with AZT, which produces anemia more often in the patients than neutropenia, that in our in vitro system, AZT was more toxic to the erythroid progenitors as opposed to the myeloid progenitors.

The most important question that we are probably looking at, can we predict toxicity at a certain dose level. Say we see an inhibition in our colony formation assay, does that translate to a concentration or an AUC in a patient where you see Grade III or Grade IV neutropenia?

One drug that we have tested on this is pyrizole

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acridine. We found a concentration that inhibited 70 percent of our colony formation correspondent to a concentration in the plasma levels that gave Grade III neutropenia in the patients. Now, this is just one drug that we have done. We need to do more drugs, such as that, where we can look at in vivo/in vitro correlations.

Another question that we can ask of the clonal assays is can they predict onset and nadir.

[Slide.]

In a study funded by the FDA Office of Women's Health in collaboration with Drs. Karl Flora and Dr. Fostino in our DPQR Division, and Dr. Don Klein, a reviewer who is doing professional development in our laboratory, and Dr. Kim Warren of Poietic Technologies, Inc., we are seeking to determine if a toxicity to a specific progenitor cell will result in a specific time to nadir.

We are using a battery of established clonal assays that model the proliferation and differentiation of myeloid precursors from the ultimate stem cell to the neutrophil. Our assay systems are a high proliferative potential, colony forming cell, which is close to a stem cell.

Then, we have a multi-potent cell that we are looking at, a colony-forming unit, granulocyte erythroid

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macrophage megakaryocytic cell, and following CFU-gm, which would be a granulocyte macrophage cell, and finally, just a granulocytic progenitor cell.

Now, looking at these, this would be the most immature of the cells, and this would be most mature, resulting in finally the neutrophil. Our hypothesis is if we have a drug that gives us a time to nadir that is very short, this progenitor cell is going to be the most sensitive to that drug. However, if we have a drug that clinically gives a long time to nadir, it is this progenitor that will be the most sensitive.

We chose alkylating agents to look at because they all share a similar mechanism of action, their clinical utility in the cancer arena, and we were able to pick several drugs that have a clinical spectrum of neutropenic timing from one week all the way out to 60 days.

Of these drugs, we have mechlorethamine, cyclophosphamide, sarCNU, melphalan, BCNU, CCNU, and the investigational agent penclomedine. Of all these agents, only sarCNU we have data on. It has only been used in animal studies. It has not yet gone into the clinic.

[Slide.]

Human bone marrow cells were exposed to the drugs for one hour. After the one-hour exposure, they are washed

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and plated in methylcellulose assay. I should point out for CFU-g and CFU-gm assays, mononuclear cells were exposed to the drug. However, for the CFU-gemm colonies and for the HPP colonies, we had to expose CD34 enriched populations.

After we plated out the cells in different concentrations, looked at colony formation and derived dose-response curves, from those dose-response curves we conducted linear regression analyses and calculated an IC70 value. This value is a percent colony inhibition. I mean the concentration of the drug at which we saw 70 percent colony inhibition.

These results demonstrate preliminary studies from 4 to 1 bone marrow samples on six of the drugs. Overall, we found the CFU-gemm progenitors to be the most sensitive species in all six drugs that we tested, however, this may be due to the fact that we have only done 2 or 1 bone marrow samples.

For mechlorethamine, due to its short time to nadir, we had early expected the CFU-g assay progenitor to be the most sensitive, however, there really isn't that much difference in these first three assays.

For melphalan, we had expected CFU-gemm to be the most sensitive progenitor, and with the one bone marrow that we have tested, we did find this to be true.

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The BCNU, we also expected the CFU-gemm to be the most sensitive and again that is what we found.

Penclomedine, overall was the least toxic of the drugs to the progenitor cells based on a molar basis. Again, we saw the most sensitive progenitor to be the CFU-gm, but due to its long time to nadir, we had expected the HPP progenitor to be the most sensitive.

[Slide.]

We still need to finish more colony assays and increase our number, our n values for all the progenitors especially for the CFU-gem, but understanding that the alkylating agents are very unstable drugs, we wanted to look at the stability of these drugs in our in vitro system. A lot of times stability is done in saline solutions or in water, however, we are putting these in an aqueous medium that contains a lot of chemicals, it contains a fetal bovine serum and all the proteins that are associated with this, and we are incubating these at 37 degrees.

So, the first drug that was looked at was sarCNU, and we had an eye-opening experience here because in water, 100 micromolar sarCNU had a peak area of approximately 1150, however, when we put the same concentration in the media at time zero, we only had a peak concentration of about 450, a peak area.

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So, this is telling us that we are losing some of our drug immediately when we are putting it into our culture media. This means we are going to have to test all of our drugs in the culture media and look at its half-life in the culture media at 37 degrees.

As a consequence, the drug amount that we think we are putting into these culture systems may not be true, and what we have to look at is the half-life and then calculate the AUC, the concentration times time for each of these exposures, for each of the drugs, and then compare that to the colony inhibitions as opposed to just the concentrations.

This has given us a valuable lesson, not only for this study, but for our future studies, and just look at drug stability in vitro, we feel it is going to enhance our predictive value of these assays and allow for a better comparison to in vivo pharmacokinetics and pharmacodynamic studies, and this will point to the fact that we need to look at the investigational agents at both biologically and clinically relevant concentrations and to utilize analytical methods that we have available to us to look at the in vitro stability and the solubility and its exposure confirmation in these culture media with or without serum.

[Slide.]

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The next study I would like to show you is looking at interspecies difference. How do we know which animal model is going to best tell us a drug is myelotoxic to humans? We have had the opportunity to look at two different DNA binding drugs that have shown in preclinical animal studies to have a great wide range of toxicity between the rodent models and the dog models.

Tallimustine and bizelesin are two such drugs. They are DNA binding and they bind at A/T-rich sequences. They are active in preclinical screens against solid tumors, and in vivo studies for both of these drugs found the beagle to be exquisitely more sensitive to the drugs than the rodent models.

The rodent was 15 times more resistant to bizelesin than the dog based on the MTD, and this difference was 100 times more for tallimustine and based on LD50, so again, for both of these drugs the question was asked which animal species best modeled human myelotoxicity.

[Slide.]

This is what some of our data look like, concentration here on the x axis and then percent CFU-gm colony inhibition here. For tallimustine we had a 4-hour drug exposure, and this is just the CFU-gm data. Here, we see with the circle, the human concentration response curve,

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and with the dotted line we see the murine.

You can see there is a concordance, there is overlap between the murine and the human sensitivity of the CFU-gm cells at these concentrations. However, you can see the great difference in the dog, it being more sensitive to this drug than the mouse or the human bone marrow.

I was just trying to think back what the difference was. I think there a 100-fold difference in the IC70 values between the human and mouse versus the dog IC70 values.

Based on this, two clinical Phase I trials have begun, one in San Antonio and at a dose of 100 mcg per meter squared, daily for three days, they found a Grade III/IV neutropenia, and a neutropenia occurred at Day 17 and recovery was at Day 21.

In another study out in Bellinzona, Switzerland, Grade IV neutropenia was found at 500 mcg/ml, and this was given once every four weeks. In the Switzerland study, they based their starting dose on the dog data because they wanted to be taking the more cautious route.

The next study here was bizelesin. This was a collaborative project with the NCI and Hipple Cancer Research Center. Again, we tested human, canine, and murine bone marrow after a one-hour drug exposure.

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Up here, we saw a correlation between the mouse and the human, and since these drugs have similar mechanistic actions, would we have seen that again with bizelesin, but, no, you can see here the human data is over to the left, the mouse data is over to the right showing its greater resistance to bizelesin, and in between we see the canine data. Only at about 1 nanomolar do we see similarities between the dog and the human bone marrow.

What is the most interesting point is where do we see 100 percent colony inhibition? Out here it takes 1,000 nanomolar to kill 100 percent of the CFU-gm from murine bone marrow, however, it only takes 1 nanomolar to kill 100 percent of the CFU-gm colonies from the mouse and from the dog and the human marrow. We are seeing 1,000-fold difference in toxicity.

As a result of this, the FDA recommended to NCI for their Phase I clinical trials to start the dose at 110 nanograms per meter squared, which is approximately 1/20th of the MTD for dogs at a daily dose. The basis of the 110 was based on the dog toxicity and the bone marrow data.

[Slide.]

What do we seek as an outcome of our program? Well, we want to validate or invalidate the use of the hematopoietic clonal assays as both qualitative and

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quantitative predictors of clinical myelosuppression.

This will probably be done in concert with an ECVAM project that is being discussed and will be underway we hope soon.

We want to be able to predict human drug safety from using cellular endpoints and compare it to preclinical animal models, and then utilize the information that we get from the hematopoietic clonal assays to help determine a safe starting dose and an escalation scheme.

In collaboration with our review colleagues, we would like to be able to develop a guideline that allows us to design, interpret the hematopoietic assay that allows us to predict human in vitro myelotoxicity risk.

Thank you.

#### **Committee Discussion**

DR. TAYLOR: The floor is open to discussion of these two topics by the committee.

Yes, Dr. Brazeau.

DR. BRAZEAU: I would like to ask a few questions first to Dr. Sistare. I am wondering if you have investigated the use of DMSO. It is a wonderful penetration agent and I wondered if you had considered using that as one of your solvents.

DR. SISTARE: We have been in discussions with Dr.

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Ray Stohl over at Boehringer Ingelheim, who is also looking at this model. We found, with TPA and DMSO, that he got no response. When you look at Tom Slaga's data with the Sencar mouse, when he used DMSO in that model, DMSO actually inhibited the ability of the TPA to induce the papilloma response.

Now, there is a couple of possibilities. Slaga suggested that DMSO may actually be acting in a positive way to inhibit the process of the carcinogenic or the papillomagenic process. Ray has suggested the possibility that DMSO may be just sort of zapping the stuff right through past the follicular layer into the bloodstream so rapidly it is not hanging around long enough, I don't know, but this whole question of vehicles is a tough one.

DR. BRAZEAU: Yes, because there is lots of vehicles that would -- you know, you have already used one of the organic solvents that are used for drug studies, you know, this propylene glycol, polyethylene glycol, and I am not particularly enamored with acetone, but, you know, you have to start somewhere. I think these are really certainly valuable studies.

There are two other issues that I thought as I was listening to your presentation - how old are your animals?

DR. SISTARE: In the first study, they were 7- to

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8-week old, and in the second study, they were 9- to 10, because that was an issue that was raised is how critical is that age. The guidelines were 7 to 8 weeks. You can only get them at 5 to 6 weeks, and then you let them acclimate for a week or two, and then you start the study.

So, we did say, well, let's stagger, let's hold off in that second study to see if it -- you know, we further resisted it, but we actually got responses in the second one where we didn't in the first.

DR. BRAZEAU: How long do these animals live?

DR. SISTARE: Twenty-six weeks, because we sacrifice them, but normally, I don't know. I am not sure how long they live.

DR. BRAZEAU: I am wondering if you used older animals. You have got animals that are growing pretty quickly, and that sort of leads me to my second area. I don't know quite the mechanism by which these will elicit a cancer response, but many of the cancer agents it is my understanding work through a free radical base mechanism, and I don't know if these do, and what you might consider -- and it has only recently come to my attention the last year -- is that many of these diets that these animals are feeding upon are very high in alpha tocopherol or Vitamin E, which is a known dietary antioxidant, and I am wondering if

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the reason you see some response in some animals and no response in other animals is a function of how much food they are consuming.

I am wondering if you did a diet low in antioxidants, if it is a mechanism that you could enhance those effects.

DR. SISTARE: That is a really good question. Other questions, one thing we were thinking about is methylation patterns, epigenetic mechanisms that might relate to methylation patterns in some animals and not others, and if you did the same kind of thing in methyl-deficient diets, to have hypomethylated, that is one approach, too, but yours is a really good one.

Other things we are thinking of, is it possible -- the way these hemizygous animals are bred, just take the homozygous female and then the parental, the FEB wild-type strain male, and then you take the hemizygous -- is it possible that one of the alleles in the homozygous female, for example, may have mutated. There is all sorts of questions here that we need to tune into.

DR. BRAZEAU: I think you have to be real careful about how much of the diet they are consuming, what is the nature of the diet. I know that previous studies with some of the lazardoid drugs in animals, you would see an effect in

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one study, and then you wouldn't see an effect the next time with some of these lazaroid drugs. They were looking at some stroke animals. The reason was is that the diets change routinely.

Animal diets are increasing in the amount of things like alpha tocopherol or Vitamin E, because they want the coats to look rich and everything else, so you have to be very consistent in the nature of your diet. There are so many complicating factors that I think you have to control how much food these animals get, you need to control, you know, and ask how much water they are consuming, because those all can impact upon your final results.

DR. SISTARE: I think those are great suggestions and the whole point being we need to define rigorously the conditions under which these studies are done, define the animal, define the conditions, dosing, all that kind of stuff, I agree.

DR. TAYLOR: Before we move from the diet issue, since I have some familiarity with the NTP program, Dr. Rao down at RTP and IHS has studied diet on the two-year rat studies carcinogenic assay, and he has developed a diet that enhances, that standardizes responses to certain index carcinogens, and you are correct, that animals, for example, that consume some kinds of diet have different patterns of

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carcinogenic endpoints as they go through that two-year study, so you might want to talk to him. You probably know him.

DR. SISTARE: I know of him. I haven't spoken with him.

DR. TAYLOR: He has published most of this in -- I have the reference, I don't remember exactly what journal -- but the diet does make a difference. Incidentally, which diet are you using?

DR. SISTARE: I forget offhand, certified purina, or something. It was based basically on the NIHS recommendation. We just kind of looked at what they had and just said, okay, we are going to this, we are going to do this exactly like that.

DR. TAYLOR: Well, there was a difference between the NIH diet and the diet that he has developed. He has enhanced this diet with certain minerals and backed off on certain other kind of compounds that he feels that inhibits carcinogen potential, so he makes the studies more sensitive, and they might pick up carcinogenesis.

Dr. Edeki.

DR. EDEKI: I find some of these studies on myelotoxicity to be very interesting and elegant. I am just trying to find out how do you apply findings from these

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studies. I know you make use of the information in terms of dose escalation when you are administering the agents to humans, but if, for example, you have a new cytotoxic drug that has a very high degree of myelosuppression, do you have a conference with the sponsor, do you tell them to withdraw it, or you just add this information to the repertoire of information or data that you have already.

Supposing, for example, the drug is also very important in terms of treating some particular malignancies even it has a very high degree of myelosuppression, it could still be used useful.

Just an additional comment. In recent years, you are aware of the number of studies using bone marrow transplantation and stem cell transfusion to get around limitations. In view of that, I mean if you have a drug that has a high degree of hepatotoxicity, how do you apply that kind of information?

DR. VOLPE: Let me see if I can remember. If a drug we find to be myelotoxic, I have to be honest that bizelesin was the first drug that we looked at for the FDA specifically, and they were just interested because a preliminary study showed such great variance in the bone marrow assays between the human and the mouse that they wanted to know where did the dog fall, and we repeated these

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studies and added more concentrations.

We just, you know, gave our data and let the reviewers know our findings. We did not sit in with the sponsor although the sponsor was the NCI, and we conducted our studies in collaboration with them. So this was a precedent drug. This was the first time we have done that.

Especially the Oncology Division, we let them know drugs that we are working on, and our data we share through seminars and just talking to the reviewers, we will do that.

You are talking about -- and the next question was like a risk-benefit type of a ratio that you have. Well, the drug may be very important clinically, but yet you are getting myelosuppression, and I think in oncology drugs, you look at a risk-benefit ratio a lot different than an antiarrhythmic drug that you are going to be taking for 20, 30 years, every day, where is the risk or does the benefit with an oncologic far outweigh its risk.

You pointed to one factor in that you have bone marrow transplantations or peripheral blood transplantations that are being given to patients, so that they can take higher doses of the drugs and you are going to kill a lot more of the bone marrow, and then you give them the reserve bone marrow from themselves or from a donor, and then, you know, help them live again.

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The other thing that is being used are cytokines, the growth factors, the hematopoietic growth factors, such as IL-3, GM-CSF and G-CSF, and this may down the line allow the clinicians to give higher doses of the drugs to the patients, allowing more cell kill of the tumor even though you are really doing some very big damage to the bone marrow, but giving them the cytokines, their peripheral blood cell counts do go back up, so that they are out of danger from hemorrhaging and fevers.

Did I answer everything for you?

DR. EDEKI: Yes.

DR. TAYLOR: Dr. Vestal, you had a question.

DR. VESTAL: I would to return to the TG.AC mouse studies just for a minute to clarify why you selected the hemizygous.

DR. SISTARE: We went with the hemizygous because that was a decision that was made by ILSI. We are not like dues-paying members to the ILSI consortium, but what ILSI has done -- and this is kind of a neat story in terms of I think it was a question that Dr. Branch asked yesterday about, you know, some sort of consortium between NIH, the FDA, and either academia or industry, or something like that -- what ILSI did was pool together the pharmaceutical industry and said, hey, here are these transgenic models,

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the ICH document opens this wide up, you guys need to get up to speed with these things, and they said, yeah, yeah, yeah, let's do it, and they all kind of contributed a pot of money, and they are moving forward with this thing.

We had our own set of questions, so we are tuned in to them, and we are comparing notes and saying here is what we want to look at, here is what you are going to look at, let's not waste each other's efforts and energies, but let's talk to each other and show each other our data.

So, they made the decision. We are not involved in their decisions in a sense of how they want to evolve these models, but they made the decision to go with the hemizygous.

The reason they did that was based on some information that Ray Tenant had shared with them, and there was preliminary data that he had had that said we used a couple of compounds that there didn't seem to be any difference between the hemi and the homo.

However, in the homo, there was a high incidence of these weird odontogenic tumors that were not treatment related, just spontaneous, we got these weird jaw tumors, so as the animals got older, they couldn't eat, they had more animals that were being lost from the studies.

So, they said why don't we go with the hemizygous

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where they don't see these weird odontogenic tumors, the animals can go the whole 20 to 26 weeks, and there seems to be equal sensitivity. But, like I say, a lot of the data that Ray had generated with 20, 24 compounds, and published on, was with the homo. When they made the decision to go with the hemi, that was another impetus for us to get involved and say we need to validate this hemi, if that is the one that they really want to move forward here.

DR. VESTAL: I would think it would be nice to compare them head to head.

DR. SISTARE: Yes, and Ray Stahl at Boehringer Ingelheim is in the middle of a study right now with head-to-head, looking at TPA and also looking at benzene in those studies, and he's -- I shouldn't say what he is finding.

DR. VESTAL: The second point is a more general point, and it was touched on with the discussion about diet. An appealing aspect of a model like this, and others, would be the potential for studying chemopreventive agents, I would think. Has that been done in any systematic way other than the diet studies?

DR. SISTARE: I have seen reports when people have something that they feel is chemopreventive -- what was this grape -- I can't think of it right now. The paper just came

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out in Science a couple months ago, and they used -- it was an initiation promotion in the skin, and they showed that this thing did prevent that. I haven't seen it per se with the TG.AC, but it would certainly be applicable in that regard.

I know that one of the first things that Leder showed was that retinoic acid blocked the ability of TPA to induce papillomagenesis, and sort of espoused the virtues of the model for that kind of purpose, as well. I haven't seen a heck of a lot done with it, but that was focused in the literature.

DR. TAYLOR: Dr. Goldberg.

DR. GOLDBERG: Dr. Volpe, was stability a major problem for you in the experiment where you looked at the degradation, and, if so, can you overcome that by constant infusion of drug?

DR. VOLPE: In the present study, the time to nadir project, sarCNU was the first drug that we have looked at stability with an HPLC assay, and this is keying us on. We have to look at the other six drugs. What we will do just to compensate and do an area, AUC type of a calculation as opposed to straight concentration.

A constant infusion, yes, that is a way to go, especially if we were doing, say, a 24-hour drug exposure.

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We would have to be able to keep that concentration up for 24 hours and say like an alzet pump, maybe just drop it in a test tube or the collimators with the bone marrow cells. That might be able to give us a constant infusion, or put this into a perfusion type system where the cells are in some sort of a vessel and the drug is constantly being infused into the vessel, and the cells are being exposed to the same concentration for that longer time period. Yes, these are considerations that we have had, and with our capability of the analytic chemists, we are learning a lot more of how to do these assays.

DR. GOLDBERG: Thank you.

DR. TAYLOR: Dr. Brazeau.

DR. BRAZEAU: With the tallimustine and the bizelesin studies, these were in vitro studies?

DR. VOLPE: Yes.

DR. BRAZEAU: I am not sure at this stage how much confidence I could put into the data until I know how stable these compounds were, because if they are very unstable in the murine model, you know, that may be a reason why you need a much higher dose, because they are unstable, so I would, at this stage, until you have got the concurrent stability data for that one hour, and the concentrations that you are going to be seeing, I am not sure how much

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faith you can put in that data at this stage because that can certainly confound the interpretation of the data.

DR. VOLPE: Right.

DR. BRAZEAU: You don't use any solvents in these studies?

DR. VOLPE: We tried to limit the solvents to ethanol and polyethylene glycol tween 80. We don't want to use anything very caustic. We try to keep the solvent concentrations less than 1 percent of our total volume, simply because the solvent is to kill the bone marrow cells, and we always have a solvent or vehicle control in a negative control.

DR. BRAZEAU: Some of my data, that I am familiar with, is PEGs and some of the tweens and surfactants can be extremely nasty to cells, so you want to limit their concentration.

DR. VOLPE: Right. I have done a study with PEG as our vehicle, and we have done it with the PEG and looked at different concentrations of PEG, and knew what concentration we started to see some toxicity, and kept our concentrations in our culture dishes with the drugs lower than that, so we are very cognizant of what the vehicle can do.

If a drug can go into solution with saline or

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media, we are thrilled; if not, we have some problems. Like bizelesin, we had to put it into a type of a solution that was with PEG, ethanol, and tween 80, and that is how it is formulated.

We also like to look at a drug as how is it formulated, how is it going to be formulated, how is it going to be given to the patients. We would like to mimic that.

DR. BRAZEAU: I think that is going to be absolutely critical.

DR. VOLPE: And going back to your stability question, this is just coming out to us recently in the past several years that we have to look at the stability of the drugs in these culture systems, how much is there.

We are going to have some drugs that are very stable, and then we are going to have drugs, like the alkylating agents, that aren't, and we have to look at stability over that time period that we are exposing the cells.

DR. BRAZEAU: When you determine these C70s, do you know that it is a linear relationship or do you need to use a log sigmoidal relationship?

DR. VOLPE: Well, linear relationship is obviously the easiest to do, and that is the first one I will do, but

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I am looking back with the alkylating agents that I know I will probably have to do a sigmoid Emax type of data, and I am fortunate to have Dr. Fred Balch back in our audience, and we will look at the data together that way.

DR. TAYLOR: Any other comments? Yes, Dr. Branch.

DR. BRANCH: One of the questions that was posed at the beginning was are we interested in seeing real data, and I think the answer is unequivocally yes. It was enjoyable to see some real data.

But I think a question that I have from seeing the real data, the real problems, is the role of using this information towards a guidance. It is very clear from the data that you are getting that you are getting results that didn't fit your a priori expectations in both systems.

The last comment of the last presentation was, well, we are going to try and develop this further for a guidance, and I can see that being the motivation for doing the research, and this collaborative venture is towards that.

I guess my question is at what stage of level of confidence in your system do you need to get before you issue a guidance.

DR. SISTARE: I was anxious to answer the question before you got to that. The information that we are

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generating actually serves several needs. For example, the ICH guidance document that is out there says, okay, industry, here are several models, let's start to take a look at these things, and sort of like giving them a green light.

Now, they need to justify which model they are going to use for their particular compound, whether it is the P53 model, TG-ras-H2 or TG.AC, they need to justify.

As an agency, we need to listen to those arguments, so we need to have some practical information in our hands that says, yeah, you are right, or have you thought about this or have you thought about that, you know, here are some real live pragmatic information exchanges to help, you know, day-to-day operations in terms of these kind of challenges that we are faced with, when do you feel comfortable enough to -- essentially, what you are asking, I guess, is when is the model validated in a sense, when do you have that confidence that the thing is validated.

I am not sure if I said it here. I have given this talk about before, and one of the first things I say is this is an evaluation, and not a validation of these models, and what we need to do is we need to get to the point where we feel we have enough information where we have evaluated the thing, where we can then embark on a validation.

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The two-year bioassay has never been validated and that is always thrown out there, but we have accepted and have embraced that.

The ideal experiment to determine whether a drug is carcinogenic or not is to put it in 1,000 humans and then get the information. You can't do that, so we accept a proximity. We look at rodents, we do two species to get more information.

Now, the question we are asking, are we comfortable enough to go to a model where we can get information in six months. The benefits are real, what is the level of risk as we go to this model of six months. I can't get give you the answer to that question that says when we will have that level of confidence to embrace these models, but it is not going to be just the FDA making that decision. It is going to the scientific community in general saying we are ready to move forward.

What Donna has pointed to, the European for the Validation of Alternative Methods has asked the same question about these kinds of assays, and they recognize the first thing we need to do is we need to establish some centers around the world that are interested in looking at these myelotox assays, and let's identify the parameters, the very things that Dr. Brazeau has identified.

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Questions of stability of the drug, hey, you can't begin to validate that model until you highlight these very issues, what are all the issues we need to be thinking about. So, we are all in this evaluation phase at this point. Now, let's evaluate all the parameters and then let's do the double-blinded study, let's do the crossovers, let's do all the things that we need to do for validation.

I guess I haven't totally answered your question.

DR. BRANCH: Given the huge interspecies variation and drug metabolism of most of the carcinogens are electrophilic intermediates, is there much work going on in trying to develop models which focus on human enzyme expression systems and maybe use the idea of surrogate markers of gene mutations, say, P53 point mutations, is that sort of moving at all or is that sort of going very stationary?

DR. SISTARE: That whole P53 model was designed around that premise that P53, it is a heterozygote animal, so he has one normal P53 allele, and then one knocked out allele, and then if you get the mutation, then, you will allow the expression of the tumor that much earlier, and that is the human P53 in that transgenic animal, so that is one of the virtues of that P53 model that is being espoused.

There is also work I believe going on -- I draw

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blanks every once in a while, I can't think of -- Dan Nibert, I believe they are trying to sort of a humanized animal, let's put human P450s in these animals and develop human metabolic machinery, as well, so there is these kind of movements afoot, but we are always going to be plagued by these questions of interspecies variations because of metabolism or targets, you know, all sorts of things, they are always going to be a nightmare and be the constant concern of how do we make these extrapolations, but we are beginning to develop tools that can answer those things.

DR. TAYLOR: Any other comments?

DR. BRANCH: Just one last question in terms of the bone marrow. One of the problems taking bone marrow is you have got a real mix of cell types in your system, and it is going to vary from one bone marrow to another.

Now, one approach to that is to enrich your cell species, go for your progenitor cells and then be able to look at toxicity and know those preferentially. Have you thought or tried, or is that a consideration to try and refine and make your model more discriminative?

DR. VOLPE: Yes. Obviously, there is going to be a difference in colony numbers between donors, just normal donors. That is why we try to keep the n value high. It is not just an n of 3. We do see wide variations between just

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the number of colonies that we get normally from a different donor and sensitivity of that donor to the drug, so that is one thing you have to consider.

In separating out the cells, we always use -- in the human assays and the dog assays -- use mononuclear cells to start off with, and I would point out in the CFU-g and the CFU-gm assays, we use the mononuclear cells.

However, when we went to the more immature cells, the gemm cells and the HPP assay systems, we had to go and get enriched for the CD34 population. The main reason there is that these progenitor cells are in such low concentration in the bone marrow, less than 1 percent of the nucleated cells in the bone marrow are these progenitor cells.

So, if we were able to just put a mononuclear population into our culture dish, if we even put 100,000 cells in there, we don't even get 10 colonies, so we have to enrich that population that we are interested in.

There is pros and cons to that where, yes, our progenitors are CD34-positive and lineage negative, however, what we would like to do is try to mimic what does happen in vivo. In vivo, you are exposing all the different cells and they may be interacting with each other, producing cytokines as such, but we do go at least to the mononuclear cells and then separate out when we look at the more immature

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populations.

DR. BRANCH: From the point of view of clinical toxicity, it's the progenitor cells that is probably the most potentially lethal.

DR. VOLPE: Correct.

DR. BRANCH: So there could be a priority towards your progenitor cells.

DR. VOLPE: Right.

DR. TAYLOR: It is time for a break. We will reconvene at 1 o'clock for the afternoon session.

Thank you.

[Whereupon, at 11:45 a.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

AFTERNOON PROCEEDINGS

[1:00 p.m.]

DR. TAYLOR: I would like to start the afternoon with Dr. Williams.

DR. ROGER WILLIAMS: I would like to take a few minutes to acknowledge the committee's contribution and very specifically two members of the committee, Dr. Edeki and Dr. Davidian. The reason I am focusing on them is that they are rotating off the committee.

It is a three-year term and their term I believe ends in October, and we probably won't have another meeting before October, so this is our chance to express our gratitude and appreciation. I will just speak 30 seconds from the heart. I really mean it when I say the Agency, the Center, OPS, and I feel very strongly about the contribution you all make to our efforts.

I won't go into it. I just want you to know I feel very strongly about it. I am going to read a letter and actually both Timi and Marie got the same letter, but it says:

"On behalf of the Food and Drug Administration and Center for Drug Evaluation and Research, I would like to express my sincere gratitude for your service to the Agency as a member of the Advisory Committee for Pharmaceutical

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Science. The commitment of time and expertise by our advisory committee members is vital to carrying out our public health mission.

"In recognition of your contribution and effort, I would like to present you with the enclosed certificate from the Center for Drug Evaluation and Research."

As you can see, it is a beautiful plaque. Our plaques have gotten more high tech over the years. I would say it is suitable for framing, but we have already sort of done that for you.

So, Timi and Marie, it has just been great working with you over the last three years, and thanks and congratulations.

I will give Marie's first.

[Applause.]

DR. ROGER WILLIAMS: Please check me because I usually give the wrong plaque.

Timi, thank you very much.

[Applause.]

DR. TAYLOR: If we had more time, we would allow you to give an acceptance speech, but not having the time, we will move on to some science.

The afternoon and final session will be focusing on clinical pharmacology topics, and Larry Lesko will give

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the introduction to the session.

### **Clinical Pharmacology Topics**

DR. LESKO: Thank you, Dr. Taylor, and good afternoon again, everybody.

We are going to have a guest speaker in our Clinical Pharmacology topic section. It is in the spirit of communication that the committee talked about yesterday. Jerry Collins is Director of the Laboratory of Clinical Pharmacology. He is going to lead off since he didn't have that time yesterday.

### **Laboratory of Clinical Pharmacology Research**

DR. COLLINS: Thank you, Dr. Taylor, members of the committee. I sincerely appreciate your accommodating my schedule and squeezing me in today.

[Slide.]

My goal today is to introduce the new members of this committee to our program in laboratory-based clinical pharmacology and to provide some update for those of you who have heard me give the same talk each of the last two years.

The first overhead tells what we think laboratory-based clinical pharmacology is all about. Most of our day-to-day work has to do with analytical methods, measuring drugs and metabolites and biofluids. If you can't do that, you don't have a program that is laboratory based.

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We would like to do collaborative clinical trials. In the current budgetary climate, it is difficult to do that. We still occasionally do that. So what we have done largely is shift much of our work to metabolic studies in vitro. We have don't have to pay our collaborators to do that. We have more control over those studies, and that has become a large part of our operation.

A very important linkage that we have developed may be the precursor or the forerunner of some of the consortia and initiatives that you have heard about yesterday and day, is our linkages to our fellow federal employees in the drug development programs that are sponsored by other federal agencies that provides the raw material for us to work on.

[Slide.]

In our current climate, we really can't be all things to all diseases, so we have tried to go for more selective excellence and just pick a few areas where we can make the most impact.

In keeping with Dr. Williams' overall paradigm of research policy and review, we long ago in this project identified our drivers. Much of the work that we are involved in has been nominated to us by the New Drug Review Evaluation staff, problems that they wrestle with on a

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day-to-day basis, and occasionally we have some projects that were selected by advisory committee members like yourselves, more in the product review area, but things that they felt we should be involved in.

What are the payoffs? Payoffs are obviously essential. As I said in the briefing document, some of our projects relate to very drug-specific issues, there is a particular NDA pending, like to have a particular set of data. Other things have to do with broad policy and results, as so many things do these days, in some kind of guidance for industry.

I personally would like to highlight the other, more traditional academic-oriented payoff of peer-reviewed papers. All of our work is intended to be published or presented publicly. Occasionally, we do get an embargo because of confidentiality, just as you folks do, but eventually, everything should be in the public domain.

In your review package, I only listed the papers that have come out of our laboratory since the last time this committee has met. I feel very strongly that these papers are not just padding for the CVs of the individual staff, but they are an element of the credibility of the CDER research program, and I think that we ought to put particular emphasis on that.

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[Slide.]

My last overhead is the cover sheet from the Guidance to Industry on drug metabolism, drug interaction issues. A paper copy is in your briefing package. For those of you who brought your World Wide Web with you, the address is on the bottom.

This project really was a joint effort. It drew upon expertise scattered throughout CDER in the review divisions, people who actually review, on a day-to-day basis, drug metabolism, drug interaction data.

We had input in this process from academia, through trade associations, and other means, from our colleagues in both industry and academia, but the roots of this project and the foundation for this guidance lays in the research program that we have in laboratory-based clinical pharmacology.

Much of the agenda that you have seen today and yesterday especially has been future-oriented directions that the Center is going. It was nice earlier this morning to hear Frank and Donna present some more present-tense, early preliminary data.

I think the emphasis for our program is already in the presence tense. In our view, over the last several years, we have been contributing to individual drug-specific

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issues that the Agency is facing. We are contributing on an ongoing basis to policy development, and we have a publicly available track record of continued consistent productivity over the years, and it nice to see sort of a balance here between a program that has been ongoing for a couple of years, programs that have just started, and initiatives that the Center has for the future.

Thank you.

DR. LESKO: I think the plan is to finish with some of the other speakers and then move into a discussion period, so I will just move forward. I have to see which set of comments I am going to make here.

### **Introduction**

[Slide.]

DR. LESKO: I want to introduce  
, and take only about five minutes to do so, the section of the committee meeting that we call Clinical Pharmacology Topics. I guess the first thing I want to say is that while they are individual topics, they are part of an overall strategic plan, and as you will see I think when you hear about some of these topics, they are very much interconnected.

[Slide.]

To frame the discussion this afternoon, I want to

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start with the challenge that really faces the drug sponsor and the regulatory review process, and that is to document and demonstrate evidence for clinical safety and efficacy, and from that information which is usually obtained from Phase III controlled clinical trials, to get an estimate of the therapeutic ratio of the drug.

[Slide.]

Now, in the ideal world, a new molecular entity is going to have no variability in response, and it follows that in the absence of variability, the drug dosing of that product becomes very straightforward.

[Slide.]

One might imagine in the absence of variability that the dose range for target populations is extremely narrow, that is, one size would fit all, the same dose would be suitable for anyone in the target population, and in fact the label would not necessarily require any particular dose range to accommodate variability.

[Slide.]

The reality is, though, in the world of pharmaceutical formulations there is reality, and I think a lot of the issues that were before the committee yesterday dealt with the area of biopharmaceutics. As Roger mentioned, biopharmaceutics focuses on product quality and

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the assurance of consistent and good quality performance of those products as measured by dissolution, bioavailability, and bioequivalence.

So, when we hear things about sameness, the issue of sameness and equivalence is all intended to reduce that variability to make dosing a little more easier in terms of the therapeutic use of the drug.

[Slide.]

On the other hand, today we are focusing in the area of clinical pharmacology, and it is perhaps as great, if not greater, a source of variability in response. Because of the combined variability between the biopharmaceutics and clinical pharmacology, we end up in practice with a dose range for target populations, a dose range in the label to accommodate a wide range of recipients of that product, and also the need to get information on dose individualization when that is necessary.

[Slide.]

So when we think of the things that we will talk about today, I think they are designed to address the issues of what do we want to know about the clinical pharmacology of the drug, what do we want to know about the variability and response, and the sources of that variability, and how can we account for it in terms of the dose in the target

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population.

We will hear a little bit about adjustments for risk groups this afternoon, and all of this information, besides supporting the safety and efficacy of the product, is intended to provide for dose and dose individualization and subsequently, the optimal dose for the patient.

[Slide.]

Now, the aspects of the clinical pharmacology program that we will be hearing about today, first of all, Dr. Gene Williams will present what we call the core information. This is the core information in pharmacokinetics/pharmacodynamics that we are thinking is essential to the assessment of the drug's clinical pharmacology.

When we talk about adjustments for risk groups, we will hear about drug-drug interactions, and the initiative that is underway in terms of guidance development there.

Thirdly, when we talk about the impact of PK/PD knowledge in drug development and regulatory review, we will hear from Bill Gillespie talking about that topic.

Finally, an initiative which ties a lot of the previous information together is going to be presented by Dr. Hepp, who will talk about the Clinical Pharmacology section of the package insert, which deals with things,

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amongst which are the dose range in the label.

Again, my introductory perspective on this is that we will be seeing a good chunk of the clinical pharmacology program in OPS and in OCPB, and I hope you will have some comments to make on it and some questions to ask about it.

With that in mind, I would like to introduce the first speaker here, Gene Williams, and he will focus on what are the questions and what do we need to know.

**Providing Clinical Pharmacology and  
Biopharmaceutic Data for Human Drug Products**

DR. GENE WILLIAMS: Thank you, Larry.

[Slide.]

What you see in front of you now is the title of my talk. It is also the title of a guidance that is in preparation by the Office. I was selected to present this to you today because I had the good fortune of being co-chair of the working group that is developing this guidance. Larry Lesko was the other co-chair.

As Larry probably made clear, our guidance is not giving detailed specific information on the wide range of things that we like to see in an NDA. Rather, the thinking is this is a home page of sorts. It gives a general philosophy of drug development and then explains at a very fundamental level the sorts of things that we might expect

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to see in an NDA.

[Slide.]

The document is divided into three sections. It begins with an introduction, and then there are two scientific sections. The first is Clinical Pharmacology. That is the one that I will address today.

Currently the document is not organized precisely the way I am going to outline, but for the purposes of the presentation, I think this is a valuable way to present it.

We divided the Clinical Pharmacology section into four different topics: Pharmacokinetics; Pharmacokinetic/Pharmacodynamic or PK/PD Analyses; Patient Characteristics Affecting PK and PD; and finally, In Vivo Drug Interactions.

[Slide.]

Additionally, as was probably evident from the title of the document, we cover biopharmaceutic topics, as well, and they are divided into three different areas: Bioavailability and Bioequivalence; Food Effects on BA and BE; and In Vitro Dissolution. As I mentioned, I won't be addressing these today, but I thought it valuable for you to know that the guidance does cover currently both topics.

[Slide.]

The Introduction of the guidance establishes a general philosophy. Among the information there is we try

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and convey the idea that what we seek is information, not a drug development scheme. It would be audacious of us to tell industry how to develop their drugs.

So, what we are trying to outline is not necessarily a path towards your goals, but the sort of information that we think is important to have in hand at the end when you file your NDA.

We also point out that what we are going to talk about is a general approach, it will vary. Most obviously, it will vary according to the clinical use of the product you are developing and the route of administration.

Also, the information we are conveying is probably most relevant to development of an NME or new molecular entity.

[Slide.]

I have organized the remainder of what I have to say in the following manner. First, I will identify the topic and the topic will be one of the four I have already listed for you within the Clinical Pharmacology area.

Once I give the topic, I will explain the use of the information or the why of why we seek this sort of information in NDA. This will be followed by a description of what exactly is it that we seek, the data that we are interested in obtaining.

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I will then add the timing of the studies, and this is not -- again, this not with the attitude of trying to dictate a drug development program, but rather because we recognize that certain information is most valuable if accumulated at certain points of time. So, we provide some guidance as to when we think it would be valuable to have this information.

We are trying to explain how we see the utility of the information and how that might fit into a development program. Then, I will conclude in those instances where such is available by saying that a guidance on the topic by itself is available.

[Slide.]

The first topic is Pharmacokinetics.

Pharmacokinetics information is useful when combined with an assessment of activity, that is, we want to measure what is active. It is useful in acquiring a PK/PD relationship. That is, if we understand how concentration relates to effect, we can develop a dosing strategy for further study, and finally, in the end, this sort of information translates to labeling.

The information we seek for agents given under multiple dose conditions would be single and multiple dose pharmacokinetics. We would want a description of the inter-

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and intra-subject variability in the typically assessed pharmacokinetic parameters, and finally, an assessment of dose proportionality and linearity.

As far as the timing, we do not give specific information as to the timing, but it is clear from the use of the information that the earlier on this information is acquired, the more valuable it has potential to be used.

We point that one study can accomplish several different objectives. It is not unusual for us to receive an NDA with a number of descriptive PK studies, and the utility of these studies is questionable. Oftentimes it seems to us that sponsors could probably do less and satisfy regulatory expectations.

We appreciate that sponsors don't always do studies for regulatory objectives, nonetheless, we think it is valuable to provide guidance and say that one study, if strategically placed and well designed, can accomplish a number of the purposes that we seek.

[Slide.]

The second topic is PK/PD Analyses. As Larry mentioned, Bill Gillespie is going to speak in much more depth as to what we believe the value of these sorts of studies are and approaches that can be used in performing them.

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In our guidance, we begin by saying that this is useful in establishing a regimen for later study. As I mentioned previously, in combination with pharmacokinetic information, the pharmacodynamic or the effect can be utilized in this way.

It is also especially useful in interpreting issues. Oftentimes there will be a change in the PK or PD for special populations and the question is what do we do about it, how important is it to put that information in labeling, is it a clinically relevant change.

Further bioequivalence determinations can take advantage of this sort of information. If a sponsor fails to meet rigid bioequivalence criteria, an evaluation can occur as to how important that is in the setting of developing an NME and what we should do about it, how we should base our regulatory decision.

Finally, as with most of this information, it eventually will translate into labeling.

The kind of information we seek begins with a measurement of effect. That can be either direct or indirect, indirect meaning a surrogate effect. If a surrogate is used, it should be justified prior to being used, possibly with consultation from us, possibly not, but if such is valued, you know, we are welcome to talk about

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it.

Finally, it should be validated. If a surrogate is selected in early Phase I, that would be unusual.

Perhaps it would be better to talk about Phase II. If the surrogate is selected in Phase II, it is useful for us to have that surrogate validated, if possible, in Phase III trials.

Finally, if there is an inability to discern a PK/PD relationship, we would ask that there be discussion. It is useful to know why the sponsor thinks that such may have been unsuccessful.

[Slide.]

One of the primary goals of performing these sorts of analyses should be to develop an optimal dosing regimen in later phase confirmatory trials. Towards that end, this information is especially valuable if accumulate early in the drug development program.

Then, it is worthwhile to continue to reexamine the PK/PD relationship in later stage trials. This can be valuable for identifying covariates in a patient population more like that, that will be encountered after the drug is approve.

Finally, a guidance on this matter, individual guidance addressing with greater particularity these issues

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is in preparation by the Office.

[Slide.]

Patient Characteristics Affecting PK and PD. It seems pretty obvious that if you understand how the drug behaves in different populations, you can write dose adjustment recommendations for the product label.

The information we seek. First, I might say that the special populations that get studied may depend in part on a knowledge of the drug. For instance, the results of a mass balance study can be useful in determining how the drug is eliminated and thus what populations are necessary to study.

Most commonly we ask for body surface area and the other characteristics mentioned here. Less commonly it can be valuable to acquire dietary or genotype/phenotype information.

[Slide.]

This isn't timing per se, but it gets at the idea of when the information is accumulated. For the most common information we would expect it to be accumulated for all subjects in clinical pharmacology and biopharmaceutic studies.

This doesn't seem to be a very stringent requirement. The most common data is accumulated routinely

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and it is a small matter to present it to us.

The less common data would only be accumulated and submitted as reasonable. Obviously, it is unreasonable to provide dietary or genotype/phenotype information in a large Phase III trial under normal circumstances.

The Agency has issued a number of guidance documents regarding the study of special populations. Four are listed here. There are not OCPB guidances per se, they come from the entire Center, but they are relevant to this topic.

[Slide.]

Finally, the last topic I will approach is In Vivo Drug Interactions. As Larry described, we have the good fortune of having Shiew-Mei Huang here to talk about this with greater specificity.

We also have the good fortune to have Shiew-Mei be a member of our working group, so we hear firsthand.

The utility of this information I might begin by saying that current in vitro drug interaction studies are insufficient to conclude that no interaction is occurring, that is, a negative result is not definitive.

The reason for this is fairly obvious. First, not all drugs are metabolized by known systems, the systems being studied in in vitro studies. Secondly, drugs can be

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metabolized by more than one system even if they are metabolized by a known system.

Finally, non-metabolic interactions are not addressed in typical in vitro studies of the type that we are speaking about here.

[Slide.]

There are a number of factors to be considered when trying to discern when it is necessary to perform in vivo drug-drug interaction studies, and which ones to perform. Five are listed here. Obviously, this is an area of much and growing scientific knowledge.

The first would be the importance of the pathway, what percent of your drug and the competing drug are metabolized by a given pathway.

Secondly, the affinity and concentration at the site where metabolism occurs in vivo.

Third, inter-individual differences in the activity of the metabolizing system.

The mechanism and time course of the interaction are obviously relevant, and finally, the route and regimen of both drugs would be considered.

[Slide.]

The timing of when this information is accumulated or how we see it fitting into development of the program is

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not expressly stated. There is guidance available on this topic. First, as Jerry mentioned, there is an in vitro guidance currently available, not directly addressing the in vivo situation, but certainly helping provide information that is useful in discerning the need for in vivo studies.

Secondly, an in vivo guidance is in preparation. Indeed, I think that is what Shiew-Mei is going to talk to us at least in part, if not predominantly about today.

That is all I have to say. Thank you.

#### **In Vivo Drug Metabolism/Drug Interactions**

[Slide.]

DR. HUANG: As you have heard from Dr. Collins and now Dr. Williams talking about the guidance, it is right here, the in vitro guidance, to talk about what is our current thinking on using the in vitro metabolism interaction technique to address drug interaction.

I had a chance to review it last May while I was still at Dupont-Merck, and we really liked it. The last AAPS meeting in Seattle, also, there is a presentation about how PhRMA really liked this guidance and how we communicate through the guidance to the pharmaceutical industry.

So, in January of this year we formed another group, a working group, to look at the in vivo aspect of drug metabolism and drug interaction.

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What I will do today is just to tell you where we are in the guidance development process and in six months time I may come back and seek your guidance on specific issues.

[Slide.]

As I mentioned, we have formed an In Vivo Working Group, which is under the CDER Medical Policy Coordinating Committee, chaired by Dr. Williams and Temple, under the Clinical Pharmacology section, chaired by Dr. Lesko, so we have input from the leaders here and the members of these two committees.

The In Vivo Working Group consists of members from our Office of Clinical Pharmacology and Biopharmaceutics. We have Dr. Ajayi, Balian, Barnette, Baweja, and Rahman. We also have Dr. Collins from the Office of Testing and Research, and we have Dr. Honig from the Office of Drug Evaluation, so we have different people from CDER.

Once we had the group formed in January, we identified issues that the group would like to address. We started to involve other members from CDER to help us address individual issues, for example, we have Dr. Marroum when we talk about study design and look at the database that the Agency has.

Then we have statisticians, we have Dr. Machado

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and Schuirmann when we talk about what kind of study design and data interpretation. When we talk about labeling, we have Dr. Hepp, and we also talk to our Special Government Employees, Dr. Venitz and Dr. Hauck, to consult on specific issues.

[Slide.]

First, I would like to review with the committee what kind of current statutory requirements on drug interaction. Here, under 21 Code of Federal Regulations, under Labeling and Contraindications, is stated the conditions where a drug should not be given when is clearly a risk which is outweighing the benefit, and the situations include the use of drug in patients because of concomitant therapy and have a substantial risk of being harmed by it. Here, we say known hazards will be stated in this section, not theoretical possibilities.

Another section that addresses this issue is Precautions on the Drug Interaction. It says that we need to give, this labeling shall give specific practical guidance for the physicians on preventing clinically significant drug-drug interactions.

It talks about specific drugs or classes of drugs with which this labeling applies to may interact in vivo shall be identified, and the mechanisms of interaction shall

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be described.

Here, although it says that in vitro and animal data do not belong here, but if they are clinically relevant, then, they will be in the labeling.

What I would like to say is based on the statutory requirements, what are getting in the submission? So, I would like to share with you two surveys that were conducted by our Office.

[Slide.]

First, is from Dr. Marroum. He reviewed the submissions that were approved between 1987 to 1991, and he looked at, out of the 98 new molecular entities that were approved between this period, about 32, or about a third, that had interaction studies. On average, there are about 4 studies with a range of 1 to 8. In this period of time, most of the interaction studies were conducted with a typical agent like cimetidine, digoxin, warfarin, and so on, not taking into account what the mechanism of interaction is. Of course, there is no information on isozymes.

If you look at another, more recent survey by our Office, and was presented by Dr. Mehta and Lesko at ASCPT meeting last March, where we look at the submissions that were reviewed in 1995, so that would include submissions probably from 1993 to 1995.

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We look at, out of the 29 new molecular entities, there are about half, which is 50 percent more than what we see in the previous period. The average study is about 6 with a range of 1 to 15.

Personally, after I joined the Agency in September of last year, I have been in the briefing, and I have seen about two dozen of new molecular entities, and I don't have the exact statistics, but I can see the studies have increased and they are more targeted based on mechanism of interaction.

Some of them have used in vitro information to design their in vivo interaction. So, the selection of interaction has improved, and the quantity of studies has also increased, but I would like to share with you what about the quality of this study, are they designed to give us the information that we would like to have.

[Slide.]

Did the studies really give us the information that we would like to have? Are we making assumptions that we should be making? For example, the typical submission that we see uses six subjects, 12 subjects, crossover or parallel. I mean can we extrapolate data from six normal subjects to a population of people with various disease states or different disease states that is being treated?

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Are we willing to extrapolate from single dose to multiple dose, and how sure do we want to be? I mean is the study large enough to tell us what do we expect in the larger spectrum of patient population?

[Slide.]

So, the working group look at the data, look at the database. We are still collecting data. And we decided, well, these are the areas we want to address in the guidance. First, I would like to talk about when the studies are not necessary or when in vivo studies are not necessary.

[Slide.]

These are the factors that we think we should consider when we are considering whether we need in vivo studies or not. These are factors that how would other compounds affect the new molecular entity. So, we need to look at the contribution of the metabolic clearance to the overall clearance. It is significant. This, we will need to use LCMSMS to get an idea of metabolism or we use a mass balance. We need some in vivo information early on in humans.

What about the contribution of particular isozymes? Even the metabolism may be an important pathway, but it would be different when the alteration of one isozyme

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for a drug which is metabolized by single isozyme versus a compound which is metabolized by a 5-difference isozyme, because you could have metabolic shifting, you could have other pathways that take over when you alter one of the metabolizing enzymes.

In talking about in vivo studies, a lot of times we make our judgment based on in vitro data, so how good are the in vitro determination of  $K_i$ 's inhibition, and are they relevant, are the concentration that we used in in vitro studies relevant to clinical situations?

The other factors we have to consider also the new molecular entities effect on other compounds, maybe because of coadministration. In this case, this factor may not be as important. You could have compound which is completely renally excreted, but yet is it affecting other compounds metabolism, like fluconazole, mostly renally excreted, yet is affecting 2C9 and 3A4 to some extent. Like quinidine is not a substrate for 2D6, and yet it inhibits 2D6, so different factors when you look at what aspect of interaction we are considering.

[Slide.]

I would just like to discuss a little more in depth on when we are deciding whether in vivo studies are necessary. We are essentially saying if we can use in vitro

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information, then, there must be some kind of in vitro/in vivo correlation.

[Slide.]

So based on the knowledge, the database we have right now, can we really extrapolate from in vitro studies to in vivo? When in vitro studies show interaction potential, I mean there is one case that we give in the in vitro guidance, and maybe we can label as such, or we can conduct an in vivo study to confirm this interaction or give the practitioner some way of handling dosing, to dose a patient safely and effectively, or maybe we want to refute and do a study to show that in vitro does not predict in vivo, and then label as negative.

The example here I have is ritonavir and pimozide. Pimozide is a compound approved in 1984, and it's only later -- of course, at the time, there was no isozyme information available -- it is only when sudden deaths was reported. When pimozide was given, it was clarithromycin, and recent studies in vitro showing that clarithromycin appeared to inhibit pimozide metabolism, which is 3A, and causing the buildup of pimozide, which increased the QD interval, causing sudden death.

So, we know ritonavir is very potent 3A for inhibitor, so we got an in vivo study. Abbott decided to

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put this in label pimozone is not contraindicated with ritonavir. So, this is a case to show in vitro data when you think it is reasonable to say that there will be an in vivo interaction that you can label as such.

[Slide.]

What about if you have in vitro data and showing there is no interaction, do we label as such? I mean how sure are we that there is an in vitro/in vivo correlation or do we need to conduct in vivo study?

These are the issues that the working group is pondering with, and these are issues that I have to briefly mention, how relevant are the clinical dosing conditions, the concentration used, are they clinically relevant?

If the interaction site is in the liver, can the plasma concentration that we are using reflect the liver concentration? What about protein binding? Theoretically, are any of the free concentrations available?

How about extrahepatic? A lot of compounds that we know, we thought there is a first pass hepatic metabolism causing low bioavailability, but recent data have shown that probably not, they are small intestine metabolism. Or maybe it is p-glycoprotein, and p-glycoprotein, even if it is expressed with 3A4, but I mean there is a correlation, and a lot of inducers also induce p-glycoprotein, so these are

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factors that we have to put into consideration when we are considering in vitro to in vivo.

Another aspect is induction. Are we comfortable with the technique right now in vitro that we are comfortable with using in vitro system to predict an in vivo condition?

[Slide.]

Next, I would like to talk about study design data analysis. In talking about study design data analysis, the group felt that these are the important factors we need to consider. Subject selection again, do we use normal or do we use patient? I mean there are instances where patient population will have different enzyme activity, for example, the AIDS group may have a higher percentage of slow acetylators, and we have to put that into consideration when we are thinking about how to design a study.

Drug administration. What kind of dose, do we use therapeutic dose? The EMEA guideline, they are suggesting maybe we should use higher than therapeutic dose to maximize the interaction effect, but oftentimes we see sponsor, they may use a lower dose than what they would recommend, and what do we do with the data?

Selection of interactants. Based on in vitro information, we might have selected an isozyme to study, but

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even within one isozyme, how do you prioritize which compound to study first, and sometimes not based on mechanism of action, because they will be coadministered, so how do you select which compounds to use? You don't want a company to do 49 studies, which we might see in some submissions.

Study design. Do we use single dose, multiple dose, crossover, parallel? Do we use placebo or open label, do we want to have pharmacodynamic measurement? Then, we ought to do a double-blind.

Data analysis. We know the drug interactions, some are variability. I mean, for example, the terfenadine study we saw, at least there is one study where they showed only 3 out of 8 subjects has increase in terfenadine level when you give the same dose, so there is a variability. You can have one subject with a high inhibition, but the other subject has none. So, how do we design a study and use analysis to capture all this information, will point estimate give us the information without concern of variability or do we use some kind of confidence interval?

In order for us to use the pharmacokinetic parameters, we are assuming there is some kind of PK/PD relationship, and Gene has touched upon it and Dr. Gillespie will elaborate on that area, but we certainly need some more

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information in that area to help us just decide whether the pharmacokinetic parameters has a bearing on the clinical end points.

So we probably need some more information.

Finally, how to use the population. We sometimes see sponsors who didn't do any specific study to address drug interaction but they used a post analysis, using a population approach to capture if there are drug interaction potential. I think the guidance we want to address is how to best design a study to give us the answer that we would like to have.

Finally, all the studies we tried to do to see what kind of information we can provide the practitioners on how to dose safely and effectively we would like to put in the labeling. How do we select interactants? Dr. Hepp will talk about this later as far as labeling.

And then what do we report in the labeling, do we put that in dose administration? Do we put it in precautions, warning? Which section of labeling do we want to put it in so that we give useful information for the provider?

And what about methods of evaluation, do we just want to say, well, there is a 15 percent change in Cmax, what does that mean to the practitioner, is it useful?

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Maybe we should just say, well, there is no interaction and there is no dosage adjustment necessary.

And there is all other factors, what do we do reporting single dose assuming it will apply to multiple dose, negative in vitro data? I mean there are some examples given, but are we comfortable in doing that and apply to most of these instances, and the effect on co-administered drugs.

[Slide.]

I would like to summarize the group's progress since January. We have identified the issues that I have talked to you, and we are obtaining early input from industry and academia. We have in-house courses to talk about drug interaction from our internal individuals, from universities, and from industry.

We will have a meeting with PhRMA at the end of May to talk about the issues and get their input even though we don't have a guidance, and we are given input in the fall workshop by PhRMA to see what kind of issues we would like to get input.

We are crosstalking with NPA, who just had a draft guidance in the drug interaction area.

So, I would like to close with the issues for the committee members. This is the issues the working group

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thinks are very important and would like to get input from you next time - when in vivo studies are not necessary, how do we select interactants, study designs, data analysis, and the labeling.

### **Impact of PK/PD Knowledge on**

#### **Regulatory Decision**

DR. GILLESPIE: Good afternoon. My name is Bill Gillespie. What I would like to do in the little bit of time I have got here is to share with you a few thoughts about the potential impact that PK/PD knowledge, particularly quantitative knowledge, could have on regulatory decisions.

I guess maybe I should comment what we are really doing today is kind of giving you kind of a snapshot in an overall deliberation and thought process that we are undergoing right now in terms of considering where does PK/PD fall in terms of the kinds of regulatory decisions we want to make.

[Slide.]

My focus is going to be on PK/PD relationships and particularly quantitative relationships, and particularly what I am not talking about is the entire realm of both pharmacokinetics and pharmacodynamics. I really want to talk about the relationship between the two, and that means

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things such as dose response and concentration response.

I want to talk about these in relationship to clinical drug development, and right now our thought processes are focusing primarily on issues related to efficacy assessment, although hopefully some of this will also evolve into considerations regarding safety.

[Slide.]

The general theme that we are working on right now is the idea that PK/PD knowledge may in some cases reduce regulatory burdens and that it can enhance the drug development process and its outcomes both by making it more efficient and perhaps more importantly, making the end results more informative.

[Slide.]

These kind of represent some of the things that drive some of the things we are thinking about. There are some guidances under development that are relevant to some of these discussions.

One is entitled "Providing Adequate Clinical Evidence of Effectiveness," and that one already exists as a draft available for comment. In fact, it is available through the World Wide Web right now.

The guidance pretty much states the way things are right now in terms of assessing efficacy. It leaves the

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door open a bit for the use of PK/PD and PK/PD modeling, but it isn't very explicit about that, and that is where the next guidance development project comes in, and that is a guidance development project having to do with PK/PD, which is kind of the central focus of the thought process we are talking about today.

Another one which ties in somewhat is there is a developing guidance on population pharmacokinetics, as well as population PK/PD. The last item here is a sort of research of method development project that is ongoing right now within our office, that has to do with using some clinical trial simulation to assess different drug development strategies and, in particular, to assess how they influence dosing or a selection of doses for specific subpopulations.

[Slide.]

The broad question we have got amongst ourselves, as well as to you, is in using PK/PD knowledge for regulatory decisions, how far do we push the envelope, how far can we reasonably take this with the current state of the art, to what extent can and should PK/PD be used for efficacy assessment.

The basic argument here is should we not make some intelligent use of scientific principles and specific PK/PD

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knowledge about relationships between things like pharmacokinetics, pharmacodynamics, and disease pathophysiology, and if are to use that, how should such principles and knowledge contribute to things like drug development strategies, study designs, and data analysis, and finally, how should they contribute to things like regulatory decisions pertaining to efficacy and safety.

Finally, to answer those, what is the current state of the art and what is the current state of opinion and acceptance on these methodologies.

[Slide.]

Here, I have identified four areas that I think are opportunities for using PK/PD in regulatory decisions. One has to do with using PK/PD knowledge as a tool for making inferences for PK studies.

The next one is the idea of in some cases being able to use PK/PD studies as alternatives to conventional efficacy trials under certain circumstances.

Three, a bit more speculatively, the idea of actually incorporating PK/PD modeling as an integral component in the analysis of large efficacy trials, such as we see in Phase III.

Finally, another regulatory application is using PK/PD modeling as a tool in developing and evaluating

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policies and recommendations.

I want to hit on each one of these briefly to sort of illustrate what we are thinking about.

[Slide.]

Now, the first one, the idea of using PK/PD knowledge, background knowledge, coupled with PK information, is a relatively non-controversial aspect for the most part, and I guess you could argue it is conventional and we probably do it on a regular basis even if only in an informal way.

The argument here is that PK/PD provides a potential basis for more rational and therapeutically relevant things like PK criteria for bioequivalence and for interpreting pharmacokinetic studies in special populations and drug-drug interactions, and then, of course, influencing the resulting labeling and dosing recommendations.

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The rationale here is that pharmacokinetics is pretty good at precisely characterizing drug disposition, but it really provides only qualitative inferences about therapeutic outcomes unless it is coupled with quantitative PK/PD knowledge.

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The argument here is that PK/PD knowledge is

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really what provides our quantitative bridge between PD and pharmacologic response, or said another way, PK/PD knowledge makes pharmacokinetics really more relevant and useful for making quantitative inferences about the therapeutic outcomes in drug treatment.

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Finally, I guess who cares? Well, some potential payoffs for PK/PD knowledge used in this way might be things like relaxed bioequivalence criteria in some instances. Certainly a more rational interpretation of our pharmacokinetic studies in such things as special populations and drug interactions resulting in better labeling and, more important, better dosing recommendations for patients.

In some instances, one might argue that it might allow for the use of a pharmacokinetic study in lieu of a large efficacy and safety trial.

[Slide.]

More on that really comes under this heading. This is the second heading I gave, and that is the idea in some instances perhaps PK/PD studies could serve as alternatives to conventional efficacy trials, and some areas where this is already considered at least to a limited degree is the idea to use a PK/PD study or in some cases

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even PK/PD knowledge plus a PK study to demonstrate effectiveness under new conditions for a chemical entity whose efficacy has already been shown under some other setting.

For example, we might use this in the case where we want to extend the application to other populations based on such factors as age, gender, ethnicity, or concomitant disease.

Also, PK/PD might be adequate in some instances for things like new dosage forms or dosage regimens. At its simplest, that is really what we already do in the bioequivalence context when we have small changes in dosage forms we already use PK in many instances as an alternative to doing efficacy trials.

[Slide.]

Another area where PD and PK/PD modeling has come into play in a regulatory setting is using bioequivalence based on PD measurements for locally acting drug products, such as topicals and inhalers.

[Slide.]

We have already got one regulatory application for this. If we take a look at the pediatric rule it says that the "FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other

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information supporting pediatric use."

In at least some cases, that other information could be interpreted to mean pharmacokinetic or PK/PD studies in children. The question comes up is could we maybe extend this same notion to other types of subpopulations, is there anything that unique about pediatrics that requires us to limit this to that subgroup.

[Slide.]

Another regulatory application is opened by another document here. There is in development part of the ICH guidelines labeled as E5 has to do with ethnic factors in the acceptability of foreign clinical data. The idea here is if you have got a drug approved in one setting, and you have shown efficacy with one group that is associated with some region or ethnicity, could we maybe extend the use of the drug to other regions by using so-called bridging studies.

Well, most conventionally, that bridging study would be a single efficacy trial in that group, but the argument could be made that perhaps a PK/PD study in that group might be sufficient to demonstrate efficacy or to at least extend the prior demonstration of efficacy to the new group.

[Slide.]

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Other places where PK/PD can come in is in new dosage forms or dosage regimens. Basically, what I have got here is suggestions that it could be used to approve cases where there is a change in rate, route, or regimen, the idea of going, for instance, from immediate release to extended release, we can ask the question does rate make a difference. Well, perhaps PK/PD can tell us something about that.

Does route make a difference? Again PK/PD might be able to tell us something about that. New dosage regimens. If you have information about PK with a given dosage regimen, and know something about PK/PD, you might be able to argue without doing full-blown efficacy trials that that new regimen is appropriate.

[Slide.]

I briefly mentioned the idea of bioequivalence based on pharmacodynamic measurements, and for those of you that were here for I believe it was the ACPS meeting, this was a major topic. It actually was a joint one with the Pulmonary group.

The idea here is that PD measurements coupled with PK/PD modeling might be appropriate for assessing equivalence on a pharmacokinetic scale for what we then termed the dose scale approach.

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This is most relevant to drugs with non-systemic sites of action, such as topicals and inhalers.

[Slide.]

Actually, what I covered just now is the notion that in some cases, PK/PD studies might be used in lieu of larger scale clinical efficacy trials. That is probably the major focus right now in thinking about the guidance in pharmacokinetics /PD.

What I want to move to now is maybe something a little bit more speculative and pushing the envelope a little farther in some ways, and that is the idea of incorporating PK/PD modeling as an integral component of initial efficacy trials for a compound.

Potential arguments for this is the end result could be more informative. By incorporating PK/PD modeling, we could glean more information about the relationships amongst dose, concentration, time, and response.

In addition, that modeling process could tell us more information about what I have labeled here as potentially predicted covariates, in other words, patient factors like age, gender, concomitant medications, and such. By looking at those in detail, we could get more information that would be relevant to individualization of treatment.

A possible argument is that these might result in

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more efficient and powerful analysis techniques for efficacy trials that might allow smaller, more efficient trials.

Currently, I would say such analysis is acceptable as adjunctive analysis to efficacy trials. The question is, is in some cases could we argue that if you have well-founded prior information about the mechanisms with which a drug acts to construct a meaningful PK/PD model beforehand, would that be appropriate to incorporate in a more confirmatory context.

[Slide.]

I will just throw this up quickly to indicate I find this particular article intriguing in terms of a way that it suggests the use of some PK/PD modeling as part of, in this case, essentially a dose ranging trial.

[Slide.]

The last area that I wanted to mention where PK/PD modeling can come into play in regulatory settings is the idea of actually incorporating it in developing and evaluating the kinds of policies and recommendations that we want it to embody in our guidances.

One particular tool that can be useful for that are simulations and, in particular, clinical trial simulations based on PK/PD modeling to assess the impact of our policies and recommendations that would pertain to

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things like study design, analysis, and regarding overall clinical drug development strategies.

[Slide.]

I will just briefly mention there is two active projects, one small, one large, that utilizes such techniques. For those of you that were here for the albuterol MDI discussion, we are currently using simulations to evaluate some of the details of the statistical analysis in the study design features for that approach.

[Slide.]

A larger scale endeavor is doing full-blow Phase II/Phase III clinical trials and simulating them to assess how well different design and analysis strategies do with determining doses for individual subpopulations.

[Slide.]

Finally, to kind of close out, just to briefly talk about what we see as some of the barriers to applying these techniques. Some of them you could label as scientific and technical.

These would include for a specific drugs, the lack of suitable pharmacokinetic measurements or insufficient knowledge about the relationships among pharmacokinetics, the pharmacodynamic measurements, and the disease pathophysiology. In those instances, we would have limited

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ability to predict the therapeutic outcomes using our models.

Another sort of barrier is more logistic, the idea that PK/PD modeling may often require more complex or difficult experimental procedures than conventional dose response or efficacy trials - things such as timed blood samples and PD measurements, so they tend to be perhaps more efficient trials in terms of length, the number of subjects, but they be more intense and more difficult to complete.

[Slide.]

Some of our tougher barriers I have labeled here as kind of cultural barriers, and these are not unique to any particular subgroup. They apply to pharmaceutical industry, individuals, to regulatory authorities, and I suppose we could say academicians also.

In some cases, we are dealing with lack of knowledge about PK/PD methods, both measurements and modeling, a general distrust of modeling and mathematical complexity. Both of these I think argue for perhaps some educational opportunities for us.

In general, I would say there is a preference for fairly simple empirical approaches that make limited use of prior knowledge about the drug and the way in which it acts, either qualitative or quantitative, and that tends to focus

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on hypothesis testing very much over estimation strategies.

I guess, just final closing, just thank you for listening to me. I don't have any real explicit questions at this time, but I look at this as an opportunity to invite you to begin making comment and to participating in some of the thought processes we are undergoing in considering how far to make such PK/PD methods.

Thank you very much.

### **Clinical Pharmacology Section of**

#### **Product Labeling**

DR. HEPP: Good afternoon.

[Slide.]

I am Paul Hepp. I am with the Office of Clinical Pharmacology and Biopharmaceutics. Today I would like to discuss a little bit about the draft guidance for industry, format and content of the Clinical Pharmacology section of Human Prescription Drug Labeling.

Others involved who have worked on this project are Dr. John Balian and Dr. Larry Lesko.

[Slide.]

First of all, the provisions for the Clinical Pharmacology section is set forth in 21 CFR 201.56. It is actually one of only 11 sections that are required to appear in the labeling.

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[Slide.]

In terms of the actual general content and format of the Clinical Pharmacology section, this is outlined in 201.57(b)(1), and it is reproduced here for you to take a look at, at your convenience. That section is what we have based our general guidance on.

[Slide.]

The impetus for coming up with this guidance, there are several factors. First of all, we have had a fair amount of feedback from clinicians that this part of the labeling may be somewhat hard to use and may not be particularly useful in all cases.

We have also had academicians and clinical practitioners who have also asked for more information to appear in the labeling. Also, we are aware that from time to time, there is inconsistencies in the label and that sometimes the presentation could be somewhat more clear.

Finally, we have a desire to improve this.

[Slide.]

So the purpose of this guidance will be to aid in developing product labeling that will be useful to practitioners who prescribe, dispense, monitor drug effects, and make dosing interventions when necessary, all towards optimal individualization of drug therapy; also, to aid in

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developing a clinician-friendly document that will enhance communication of a sometimes very complicated set of information; to increase the practical value of the labeling and also to encourage and also to encourage wider use and more frequent use of the labeling.

Finally, we would like to bring about a consistency in this part of the labeling.

[Slide.]

This is an outline of the general Clinical Pharmacology section that we are proposing in this guidance, and it will be broken down into an Introduction, which will mostly include what was discussed in the Purpose previously.

It will have a Highlights section, which will be something new, which will contain mostly very critical information. Then, there will be a detailed information section, which will include these various elements here - mechanism of action, pharmacodynamics, pharmacokinetics and ADME, special populations, drug-drug interactions, pharmacokinetic and/or pharmacokinetic graphs, and also a pharmacokinetic table.

[Slide.]

Starting out with the Highlights section, this section will be intended to be a concise, clinically relevant summary of clinical pharmacology of the drug as it

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relates to safety and efficacy.

We hope that it will be useful in quickly locating important PK or PD information when a complete reading of the labeling is not necessary. It is not intended to be a substitute for the complete section of the Clinical Pharmacology Labeling.

Included in this Highlights section will be pharmacologic class, mechanism of action, pharmacodynamics, pharmacokinetics and ADME, special populations, and drug-drug interactions.

[Slide.]

Moving on to the more detailed section of the labeling, we will start out with mechanism of action. This will be a summary of the mechanisms or the believed mechanisms related to safety and efficacy. Non-clinical data should only be included here if it would be important to the use of the drug.

[Slide.]

The next section would be the Pharmacodynamic section, the pharmacologic effects thought to be related to clinical effectiveness and toxicity. Included here would be dose or concentration response relationships, both efficacious and toxic; variability of response; time course of action; therapeutic window if this has been established;

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information on therapeutic drug monitoring if this is necessary; PD response differences in special populations. Also, tolerance with withdrawal effects would be mentioned here.

[Slide.]

The Pharmacokinetics and ADME section of the labeling would include clinically important PK parameters such as Cmax, Tmax, clearance, volume distribution, and half-life. This would appear in the text and later on there would be further PK parameters that will appear in a PK table.

The following elements - absorption, distribution, metabolism, and excretion would also appear in this section. Again, in vitro findings and animal study results would be included only if relevant to therapeutic usage of the agent.

[Slide.]

The next section that would appear would be Special Populations. This would be pretty much limited to clinically relevant PK and/or PD information in populations, such as geriatrics, pediatrics, gender, different ethnic groups, disease state groups, smokers, drinkers, and overdose patients as a population.

Clinically important special population variations should be included in other areas of the labeling as

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appropriate, and this would include Warning section, Precaution section, Contraindications, or Dosage and Administration.

[Slide.]

The next section would be for Drug-Drug Interactions. This would be drug interactions on the subject drug, and this could come from either in vitro or in vivo sources, which involve absorption, distribution, metabolism, excretion, protein binding, or pharmacodynamics of a drug.

Effects of the subject drug on other drugs should also be included here, and again this could come from either in vitro or in vivo sources.

Clinically important interactions with recommendations in terms of dosage adjustment or contraindications should appear in the other parts of the labeling, such as Warnings, Precautions, Contraindications, or Dosage Administration. This should appear in the alternate drugs labeling, as well, if it is important.

[Slide.]

Another section will be a Pharmacokinetic Parameters table. This is to provide information without cluttering the textual parts of the labeling.

It would summarize PK parameters for the drug, also in addition, significant active moieties, such as

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active metabolites and in some cases enantiomers.

This information may be necessary in initiating loading doses, calculating chronic dosing, and making dosage titration.

[Slide.]

One of the section, which may be an optional section depending on the drug, is a graph section, and it could include both pharmacokinetic and PK/PD graphs. They could predict PK performance and/or important PK/PD relationships if they aid in optimizing therapy.

Also, variability indicators should be included here to help interpret the graphs.

[Slide.]

The current status of this guidance. It has gone through quite a thorough Office of Clinical Pharmacology and Biopharmaceutics review. It has had a fair amount of review within the Office of Pharmaceutical Science. The Office of Review and Management is currently looking at this, and today it is being presented to your group, mostly to make you aware of this.

Some next steps that we are considering is perhaps an expert meeting, maybe another presentation to this committee in September or October to actually get your comments, perhaps a presentation to the Medical Policy

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Coordinating Committee.

We could make the draft available to the public and trade groups through Internet. This is something that we commonly do. It may be published in the Federal Register for comment. Then, we would incorporate any comments as necessary and hopefully issue the guidance.

Thank you very much.

DR. TAYLOR: Thank you very much for that discussion. That has given us a lot of food for thought and I am sure will generate some robust discussion.

The floor is now open for committee discussion of these items. Dr. Edeki.

#### **Committee Discussion**

DR. EDEKI: Just a question on the in vitro metabolism studies, these studies are done during the preclinical phase of the drug. How do you ensure that the concentrations you use are relevant to what is the eventual plasma concentrations? If the eventual plasma concentrations are kind of different, do you repeat the in vitro studies? I am referring to instances where these studies are done before the drug is given to man.

DR. COLLINS: Well, we certainly think there is tremendous value in doing these studies before they are given to man although it does not appear that the majority

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of data that we review actually are conducted prior to the first studies. By the time most of these studies are conducted currently, a Phase I trial has already been done and something is known about the human levels.

If we did perhaps what you suggest, and do the evaluation before first time in human studies, then, I would think that the circulating levels in animal species would be the preliminary zero order estimate of what the relevant concentration should be.

If subsequently you find out that there is a large disconnect between concentrations in animals and concentrations in humans, that is pretty interesting information in itself.

DR. TAYLOR: Dr. Brazeau.

DR. BRAZEAU: I have several questions and comments for Dr. Hepp.

In the labeling, will there be any place for like some of the statistical pharmacokinetic parameters like mean absorption time and mean residence time?

DR. HEPP: That sort of information could appear in the table, the pharmacokinetic table, so there would be a place for that.

DR. BRAZEAU: What I didn't seem to see or I wasn't clear, where would food or nutrient interactions with

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drugs be put in this labeling?

DR. HEPP: That could go in several places. One could be in the absorption section if it was an absorption interaction. If it were a metabolic interaction, it could go in the metabolism section.

DR. BRAZEAU: I might suggest that if there is significant food effects, that that may even warrant --

DR. HEPP: A special section?

DR. BRAZEAU: A separate section. The other thing is you were talking about under the pharmacokinetics, you might talk where a drug has got some active metabolites or enantiomers, and I would think that that should go up early in the labeling, because if a drug has active metabolites, I think that is the kind of thing that the clinician or somebody might want to know early in reading the monograph versus way at the back, particularly if the metabolite is active and the parent compound isn't, or if there is reversible -- you know, just a general statement to say that the active metabolite of this species is.

DR. HEPP: If that was important, we could put that in the Highlights section at the beginning.

DR. BRAZEAU: I have one question for Dr. Gillespie. In your studies here, do you have any plans to look at just the variability in certain simple

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pharmacodynamic parameters, like the EC50, because it has been suggested that the variability in those parameters are going to outweigh any variability in pharmacokinetic parameters.

DR. GILLESPIE: I guess the short answer to your question is probably yes. To make one thing clear, we are not actually doing studies ourselves, but I think that variability in the pharmacodynamics should be as important to us as the pharmacokinetic variability, especially if we are talking about PD n points that we believe are relevant to therapeutic outcome.

DR. TAYLOR: Dr. Goldberg.

DR. GOLDBERG: Dr. Gillespie, what thought has been given to tying surrogate markers to pharmacodynamic measurements?

DR. GILLESPIE: I am trying to think of all the various places where that has come up in the Agency. I am not going to be able to give you any definitive response. There are several sort of sites within the Agency that are considering that issue. In fact, it has been considered historically for quite a long time, but it is a question that is being asked a lot right now within our office.

DR. GOLDBERG: I don't know enough about it, but my feeling is that surrogates might be a less variable than

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the EC criterias for dynamics. I thought it would be an interesting place to look at that.

DR. GILLESPIE: It could be although probably more often than not, that PD n point where we are estimating the EC50 is in many cases going to be in some sense as a surrogate.

DR. TAYLOR: Just as a general comment -- this is for Dr. Hepp -- on the labeling issue, there are two issues that came to mind during your discussion. One is that as I look at your second slide in terms of what else is in the labeling, I am a bit concerned that this Clinical Pharmacology section, while I agree with everything you have presented, and I would love to have that kind of labeling available to me, is going to make the labeling quite lengthy. I just want you to comment on that.

The second comment is that given that most physicians who are practicing these days were trained before we knew a lot about pharmacokinetics, and so forth, I wonder what the impact of having all that information available to them in the labeling will be.

I am not trying to dampen your efforts, but I am trying to be practical when you come out with such an extensive document really in the labeling. I wish there was a way that I could ensure that all of your efforts would

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really go to good use on this population of individuals.

DR. HEPP: Actually, I believe that all of the information that was presented, or most of it, currently it does show up in labeling, maybe in a different format or order, but this approach we hope that this will organize it and hopefully, really even shorten the label.

The pharmacokinetic table that we mentioned will actually remove a lot of that information out of the text of the labeling and put it in a table, so as not to clutter the text part.

In terms of usage, I think you are right. I think there will be groups that can use this information and other groups that won't use it for various reasons, and I think it will be an education issue to try to bring everybody up to using that information.

DR. TAYLOR: Initially, I hope you will have some in the label that you will suggest that there will be something that will do some education, as well, to make it useful for those individuals.

I mean a lot of docs don't know what a Cmax or T1/2 or V is, and I don't know where to put that, you can't put that in the label, too, but somehow we ought to get that message out to people, as well. I don't know whether you put that into an FDA Bulletin or Internet, or somewhere.

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DR. GONZALEZ: I would like to comment on that very issue of what the physician is capable of understanding or comprehending, but being involved in medical education on a daily basis, and participating, as many of us do, in symposium, I think it is the responsibility to some extent of the clinician in practice to stay abreast of the current changes. I am not disagreeing with some of your comments, but we can't hold science hostage to the ignorance of the practitioner. If the practitioner has been out for a long time and doesn't really understand where we are today in our scientific approach, then, I suspect he or she is having a difficult time establishing a good practice or doing the best for their patients.

DR. TAYLOR: Well, I can tell you that -- you know, I agree with you that we all have a responsibility to do that, but there is certainly a lack of disconnect in knowledge base in physicians, and it is pretty common.

DR. GONZALEZ: I agree with you.

DR. TAYLOR: Dr. Zimmerman.

DR. ZIMMERMAN: As a pharmacy educator, I would say that one of the things that we are trying to do is teach pharmacists, clinical pharmacists and based very strongly in pharmacokinetics, so hopefully, the clinical pharmacist is a resource for the practicing physician, as well.

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DR. VESTAL: I was just going to add a little more to this discussion. I think what you say is correct. Many physicians are not able to cope very well with this kind of information, and yet I also agree that we shouldn't science hostage to the ignorance of health care providers.

So, there is the possible benefit that with more of this kind of information in the labeling, even if the detailed information is relegated to the last part of the labeling, it may, nevertheless, stimulate our medical schools to provide more support for education. One might hope that that would be true.

I think that this reorganization of the labeling has been a little bit controversial, at least in one or another context. I have heard some concern expressed that we are relegating all of this information to the end of the labeling, suggesting that it is all not that important.

So, I think I would like to just emphasize that I think this makes the content of the Highlight section very important, what is in there, and that it should not be excessively diluted.

DR. TAYLOR: In fact, in the Highlight section, you might even box it or somehow make it stand out, so that for those individuals who will not read the complete label, that certainly the key information they can go directly to

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it and it is actually they are pointed to it, and the really critical relevant information be included.

Dr. Branch.

DR. BRANCH: In terms of an additional comment on the education side, I think that the attempt to make something systematic will help from the perspective of people getting used to seeing the information provided in the same format.

I think the second part is that a clear exposition here is an incentive for industry to collect that data and then they have the in-house information from which their reps do the education, and I would hazard a guess that 80 percent of continuing medical education of people trained 20 years ago comes from drug reps, not from anyone else.

Finally, I think that if lawyers can understand it, I think physicians have to understand it, so I actually think that there is really not much of an issue in terms of comprehensibility to it.

DR. TAYLOR: Roger, did you have a comment?

DR. ROGER WILLIAMS: Actually, I have several. I might ramble a little bit, but I will try to be fairly brief.

First of all, I would like to put this in some context, because we had, I would say, an excellent series of

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presentations, but a little low key, but I actually think there are some revolutionary aspects of what we are talking about here today, and let me see if I can get to them.

I think there is a debate in the Center now between these kind of early clinical pharmacology PK/PD approaches, perhaps with a good mechanistic understanding of what the drug does.

First, there is the later phase empirical studies, and I think that debate will continue to exist in this CDDI forum, but in a way I think it may be not so much a debate as just getting everybody to come to a good understanding of what we are talking about, and I think the payoff could be extraordinary.

There may be some early phase studies kept to a minimum where you generate optimally the kind of information we are talking about in a relatively small number, and then if you go to your later phase studies, I think we need to look to the ICHE-1 document, which postulated that perhaps you could do adequate safety for most chronically administered drugs, say, in an n of about 1,000.

So let's say we now have a data set -- and I am using rough numbers, of course -- 1,500 people. That is substantially smaller in many instances than the data sets that we sometimes see now, and I think the savings in terms

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of expense to industry, the time it takes to get a drug studied could be extraordinary.

That is one aspect of this. You see we are all the time struggling with our CFR that had that magic "s" word, where it said based on adequate and well-controlled studies as opposed to one study. I think we are trying to think via this guidance document on the efficacy standard, you know, what are good general approaches to documenting efficacy and dose, and dose individualization.

Now, there is another aspect of it which I think is intriguing, and you heard it alluded to in the course of the presentations, which is extension to other populations, and, of course, you heard it mentioned, gender, ethnic, elderly, age, all that stuff. In the ICH context, it occurred with extension -- and I will single out Japan, because Japan sort of had the thought that an island country where the populace was different, you know, that was their thesis, that the entire clinical data set sort of had to be repeated when the drug came into Japan.

I would say ICH has worked very hard in this E5 document to develop the concept of a bridging study or set of studies, that I think has an enormous payoff to a global manufacturer who wants to get into different markets.

Now, I was always very sympathetic to the Japanese

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because you have to kind of say, well, this country too a long time before we would start accept clinical trial data from Europe, and I think Japanese equivalently had sort of a sense that they want to be very cautious, too, but I think this E5 document is breaking down some of these barriers and allow, you know, focus studies to bridge into different populations and different ethnic groups.

A couple of quickies. The Agency does, of course, rely on surrogate markers to approve, you know, blood pressure is a surrogate marker, cholesterol is a surrogate marker, so to me the issue of surrogate markers is not a big one. I think the challenge is always finding a good one.

We have seen the debates about CD4 and AIDS, not being so good, and maybe the current viral load as being better, and we have been burned a couple of times. I think the Center feels that, for example, with some of the antiarrhythmics, relying on arrhythmia suppression led us down some damaging paths. So, the surrogate story is not over yet, but it is a mixed story.

I will just draw the committee's attention to this individual therapeutic window which Bill talked about, and I very intrigued about getting good PK/PD data that allows us to set our goalposts more rationally, and the committee may remember that that was a substantial part of the individual

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bioequivalence debate, you know, what is 80 to 125, and where does it come from, can we do better.

So, I think you saw some glimpses today of how we can do better.

Now, I could talk a lot more you can tell, I don't want to get wound up, but let me conclude by saying this. First of all, I really want to congratulate Larry and his group. You know, they have worked very hard over the last 12 to 18 months to kind of delineate the issues, and I wouldn't say they have all the answers yet, but just forming a coherent story of, you know, general approaches and methodologic applications I think has been a real achievement of the Office over the last 12 months.

I think they are ready now to engage with the world, and you saw some of the mechanisms of engagement, to carry on the discussion. I want to give them a lot of credit for doing this.

You know, if you talked to people two or three years ago in the Office, you would have seen this wisdom there. I mean there is a lot of talent in the Office, and there has always been a lot of talent in the office, but it is a different to pull it all together into kind of a consensus wisdom, if you will.

I might argue that that is very critically

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important because the Clinical Pharmacology group in the Center has to work closely with those 13 new drug review division physicians, and you could imagine if you had, you know, each physician having their own view and then each, you know, clinical pharmacologists having their own view, the label would tend to be chaotic, you know, everybody would emphasize something different, and, you know, what is important and what is not important.

I think you are seeing a terrific value here that will pay off in terms of a more coherent label, better studies, et cetera, in the coming years.

Now, I will close by saying I was kind of whispering to Larry to see if he wouldn't mind saying this, but I would imagine perhaps the next advisory committee meeting might be a two-day meeting where we focus just on clinical pharmacology topics, and we watch the evolution of some of these guidances and we would try to draw in the physicians from the Center, you know, who ultimately have to buy into this in a very critical way.

Of course, I am talking about Bob Temple, the five O directors, and perhaps those 14 division directors. I think it could be an incredibly exciting advisory committee meeting.

DR. GONZALEZ: I would like to make two comments.

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First of all, I think Larry and his group are really, as Dr. Williams said, to be commended. I have not seen these issues presented as clearly as I have seen them today, and it goes back to Robert Taylor's comment, Dr. Taylor is right, people don't read like we expect them to read, and people don't keep up like we expect them to keep up. Part of it is, though, that we have made this mumbo-jumbo pharmacokinetic/pharmacodynamic of interest to us, but not of palatable liking to others. I think Larry and his group have changed that.

Now, I think if you go a step further -- and this is a comment back to Dr. Williams -- the package insert is still kind of ungodly and maybe an executive summary of that pertinent information, which we are working so hard to bring to the forefront, should really be placed at some point in the package insert, so that the non-reader, who is going to look for the 30-second sound bite, goes for it and there it is, what he or she needs to know about using this drug, and given all the pertinent modern age data is readily available.

So, I think as Larry and his group have brought PK/PD to the forefront in a palatable way, we need to have the package insert catch up to them.

DR. TAYLOR: That is what I meant.

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Any other questions? Yes.

DR. DAVIDIAN: One question for Dr. Gillespie.

I just wonder -- I think it is really neat to get some of this more, you know, modeling approaches into drug development and into the regulatory process. From a statistician's point of view, I feel obligated to bring this up.

I am wondering, say, in population analysis, and so on, you know, from my experience using different methodological approaches, and so on, can lead you to perhaps ultimately different models, for example, the covariates you might include, and so on.

I am wondering, in your thinking about developing guidances for, say, population PK/PD, how the Agency might resolve, for example, a sponsor coming forward with an analysis where perhaps certain covariates appear as important, yet, by another method, those same covariates might not enter the model in the same significant way, and how would you resolve that and how would you proceed in that situation.

DR. GILLESPIE: You guys don't ask easy ones. Actually, much of what you are asking is probably not going to crop up in the PK/PD guidance in a direct way because it is probably going to be addressed in a population PK

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guidance.

One of the most critical things to us I think in population methods and modeling in general is kind of communication with how you got to the end result. Especially if it is an exploratory modeling procedure, sort of how you got there often determines where you get to, and so we need enough information about the model development process to understand what were the either explicit or implicit hypothesis tests, if you like, that you were conducting all along to include or exclude covariates, you know, what is the rationale for certain choices in terms of your model, how you brought that covariate in as opposed to a linear or a non-linear approach, what were the probabilistic assumptions, things like that, was there any rationale or was this just kind of your SOP for doing it.

The more we have of that, the more we can probably make a reasonable judgment, but at this point, I don't think we are at the stage where we could give an absolute this is the way, you know, in extremely absolute terms as to what is an appropriate covariate, what isn't.

In the end, I guess one of the more critical elements is going to be not only does that covariate come in, say, significantly, but is the difference big enough for us to be concerned about and to act on in any way in terms

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of either labeling or dose.

DR. TAYLOR: Yes, Dr. Zimmerman.

DR. ZIMMERMAN: I just have another question going back to the use of surrogate effects. In Dr. Gene Williams' presentation, you talked about the fact that the surrogate, whatever it is, should be justified and validated.

Now, to me, my reading of this is that it means you have to -- well, for example, suppose you are looking for -- the sponsor's drug has effects on osteoporosis, and you can't wait 10 years to see if it actually works, or if the effect is on delaying the time to progression for a slow-growing tumor and you can't wait that period of time, but when you talk about validation, to me it means my short-term effect is validated by the long-term effect, I mean how do you deal with that?

DR. GENE WILLIAMS: I will begin by saying that I trust that Bill will straighten me out if I don't do a good job here, but I think the idea is that, first of all, there should be considerable forethought as to selection of a surrogate. That may involve some intellectual difficulty, but it is pretty straightforward that you should think about what you are going to measure.

Once that occurs, oftentimes there will be opportunities for validation within the program, and that is

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most specifically what I was speaking about. In other words, if you are thinking of a lot of your clinical pharmacology information coming from relatively early phase trials, Phase I and Phase II, where you have small numbers of individuals and a surrogate on which you base some decisions, oftentimes in Phase III you may have opportunity in conjunction with confirmatory trials to elucidate whether indeed that surrogate is a reasonable marker for what is of true clinical interest.

So, I think the idea that we are trying to convey is in those situations where this fits, we would like to see that, but the examples that you are talking about are considerably different. You are saying that validation, there is little potential for validation within a Phase III program and we are not specifically addressing that, that is whole other topic.

DR. TAYLOR: Dr. Branch.

DR. BRANCH: I had a question for Dr. Huang. You made a comment as you were talking about drug interactions that, in the analysis side of it, there may be some parallel issues with the bioequivalence area, and I was wondering in this question of confidence interval estimates, whether you have given thought to the fact there is a real major difference between looking at adverse effects versus the

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desired therapeutic effect.

If you are getting a mean change, that is really where you are targeting your desired therapeutic effect, and that is what bioequivalence is really targeting, but adverse drug reactions, you get tremendous intersubject variation, so for drug interaction that has the potential to result in drug interactions, consideration of the outlier rather than the mean becomes the focal point of interest.

In your considerations, are you pulling in your statisticians? I am thinking of the presentation that was done yesterday, that was actually starting to go into some of the statistical background of that, but are you getting statistical input into how to do the analysis?

It would be very interesting to take your 14 studies that were done last year and actually you have got some real live data, and be able to apply different statistical approaches to some data and see what would be the recommendations based on do you really need this sample size, do you need 6 or 12 or 20 or what have you.

But I think that a statistician's involvement would really help and having some real data could contribute to that discussion.

DR. HUANG: Yes, we do have statisticians involved in our working group, Dr. Machado and Don Schuirmann. We

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have quite a few sessions and discussion. Actually, tomorrow we will have another discussion on the concept of using equivalency as a parameter to look at whether there is interaction and that that may apply to food effect, how do you say there is no drug-food interaction, or maybe even you may know -- or hepatic impairment, do you consider there is a difference or not a difference.

I mean the goal is, based on statutory requirement, we want to prevent drug-drug interaction. Even sometimes you have positive drug-drug interaction, but if you want to prevent, then, maybe we want to have a clear idea of whether there is an interaction or not.

If we want to define there is no interaction, then, maybe we can use a certain statistical way to say there is not an interaction. If there is an interaction, then, we can quantitate to say, well, what is the magnitude of interaction and how do we base data to make dosing adjustment, dosing recommendation.

But if we can first square away, say, well, there is no drug interaction, if we can answer that question, then equivalency concept may work. I mean we don't have to use AD125, it depends on your therapeutic index. You may be 200 percent, 71-30, 52-200. If you can have some information, some PK/PD information, that may be helpful.

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I mean we do have to give some information in the labeling, just say 13 percent may not be helpful. If those are not clinically relevant, we like to say there is no drug interaction, so that is why we are trying to see if we can use that equivalency concept to help guide the labeling.

DR. TAYLOR: There being no other comments, Roger, do you have any comments that you would like to make?

DR. ROGER WILLIAMS: Just very briefly. I think in some ways this has been a unique advisory committee meeting, and I would say it is because we haven't been dealing with contentious industry issues with a lot of industry present, and I might say that I think it has been a low-key discussion, but I think one of the most effective I have seen.

I just want to thank the committee, and I appreciate the chance to be thoughtful without a lot of hubbub going on.

DR. TAYLOR: Thank you.

I would like to thank on behalf of the committee, and I think I speak for the committee on this, is thank the Office of Pharmaceutical Science, in fact, give them a hand for really organizing a very dynamic program.

[Applause.]

DR. TAYLOR: Even since the last committee

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meeting, I can see tremendous growth in what the Office is doing, so you are to be congratulated and, Roger, keep up the good work.

With that, I would like to adjourn the meeting and see you at the next meeting.

[Whereupon, at 2:52 p.m., the meeting was adjourned.]