Food and Drug Administration

Center for Biologics Evaluation and Research (CBER)

Cellular, Tissue and Gene Therapies

Advisory Committee (CTGTAC)

OPEN SESSION

July 26, 2016

FDA White Oak Conference Center
Great Room Salon A
Silver Spring, Maryland

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PROCEEDINGS (1:00 p.m.)

Agenda Item: Welcome and Call to Order, Janie Kim, Pharm.D., Designated Federal Officer

DR. KIM: Welcome to the 65th meeting of the Cellular, Tissue and Gene Therapies Advisory Committee. My name is Janie Kim; I am the Designated Federal Officer for this committee. Denise Royster is the Committee Management Specialist and she is out front. Welcome on behalf of FDA and the Center for Biologics Evaluation and Research. We would like to welcome everyone to this meeting.

Before I read the conflict of interest statement and make some administrative remarks, I would like everybody to introduce themselves around the table and then we will try again on the phone to see if we can get some audio. We will start with Dr. Beaucage.

DR. BEAUCAGE: Serge Beaucage. I am in the Division of DBRR-IV, and I am currently the Acting Chief.

DR. WEINBERG: Wendy Weinberg. I am the Chief of the Lab of Molecular Oncology in the Division of Biotechnology Review and Research-I.

DR. CLOUSE: Kathleen Clouse, Director, Division of Biotechnology Review and Research-I, in OBP.

DR. KOZLOWSKI: Steve Kozlowski, Director of the Office of Biotechnology Products.

DR. MAX: Ed Max. I'm the Associate Director for

Research for the Office of Biotechnology Products.

DR. JOHNSON: Gibbes Johnson, Acting Director, Division of Biotechnology Review and Research-IV.

DR. KIM: Also, on the phone are CTGTAC members Timothy Cripe, who is the Chair, who we can't hear; Ann Zovein, Catherine Bollard, David Bartlett, Jan Stegemann and Janet Wittes, Leisha Emens, Liz Pluhar and Ole Isacson, and our acting consumer rep, Stephen Rose, and a couple of named guests I just have phone numbers for; I don't have their names logged in. With that we will wait and hopefully, the technical issues will be resolved as we go along.

We will begin today's meeting with an open session that is open to the public, followed by an open public hearing portion of the meeting, both of which are available live on Webcast and is being streamed as we speak.

It is important to make sure that no personal actions or any other confidential information is intentionally or inattentionally disclosed or discussed in the open session. If there are no comments from the public the meeting will then go to closed session, and that portion of the meeting will not be webcast.

For the closed session, the FDA staff members being evaluated by the site visit report members will leave

the room, and the industry rep, also, Dr. Dale Ando, will also leave the phone because it is a confidential, closed meeting.

For those on the phone, please remember to identify yourselves before speaking and to mute your phones when you are not speaking to help minimize any background noise so that the transcriber can pick up everything that is being discussed. Thank you.

We also remind the committee that the information related to personnel actions for FDA staff is confidential and must not be disclosed or discussed in the open session or with any other personnel outside of the closed session meeting.

I will now go to the Conflict of Interest statement.

Agenda Item: Conflict of Interest Statement, Janie Kim, Pharm.D, Designated Federal Officer

DR. KIM: The Food and Drug Administration is convening today's meeting of the Cellular, Tissue and Gene Therapies Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. All members of the committee are special government employees and are subject to federal ethics and conflict of interest laws and regulations covered by, but not limited to, those found in 18 USC Section 208 and Section 712 of the Food, Drug and

Cosmetic Act.

FDA has determined that the members of this committee are in compliance with the federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees or regular employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant the waivers to special government employees and regular employees with these conflicts when necessary.

Related to the discussion of today's meeting, members of this committee have been screened for potential conflicts of interest of their own as well as those imputed to them including those of their spouse, minor child and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties as well as primary employment.

Today's agenda involves discussion and review of confidential personnel information where disclosure would constitute an unwarranted invasion of personal privacy.

The committee will discuss reports of intramural research programs and make recommendations regarding the personnel staffing decisions. Based on the agenda for today's meeting and all financial interests reported by the committee members, no conflict of interest waivers have been issued in connection with this meeting.

We want to remind the committee that the information discussed during this session is confidential and must not be disclosed to or discussed with others outside of this forum.

The industry representative for today's meeting is Dale Ando. Dr. Ando works for Sangamo Biosciences, Incorporated. As an industry representative for this committee he will be representing the interest of the industry as a whole and not any particular company or business entity. Thank you.

We will go to our first presentation from Dr. Kozlowski.

Agenda Item: Center for Drug Evaluation and Research, Steven Kozlowski, MD, Director OBP, and Edward Max, MD, PhD, Associate Director for Research

DR. KOZLOWSKI: While we're waiting I would like to thank the advisory committee. We really appreciate the time and effort that goes into the evaluation of our research programs.

The slides are not up yet, but what I plan on doing is talking about the OBP organization and its regulatory responsibilities briefly and then transition to Dr. Max, our Associate Director for Research, in order to talk a little bit about the research program.

I talked about our organization and regulatory role. We review a variety of products including monoclonal antibodies and various variants of monoclonal antibodies, and also other therapeutic proteins including enzymes, cytokines, growth factors and toxins. An example of those products is shown.

We, in the past, were organized into two divisions, one which dealt with antibody-related products and the other with other therapeutic proteins. We have reorganized into four divisions, each of which can review any of these products. In this slide we show the four divisions and the labs associated with the people being reviewed today, which are in the DBRR-I and DBRR-IV, so you can see where they fit into our organization.

As a broader view of our organization, each division has a review chief who supervises three to four teams of five full-time reviewers who do review work alone. Then we have two labs generally in each division with two lab chiefs, each of which supervises their own lab and one or two principal investigators. As you can see in both

divisions, the labs, the Laboratory of Molecular Oncology where Dr. Weinberg is the Chief and Wen Jin Wu is being evaluated, and the Lab of Biological Chemistry in the fourth division where Serge Beaucage is the lab chief and Baolin Zhang is being evaluated for his research program.

OBP products, aside from having many different structures, have a variety of clinical indications -- many oncology indications but also cardiovascular and neurological indications, autoimmune and rheumatic diseases, GI, derm and anti-infectives, too. So far, we do not have a licensed product for a psychiatric indication but I am sure that will arrive soon.

These products have increased a lot over time. There have been biological products for a long time, but the 1980s really was the herald of recombinant protein products, and in the last two full years, 2014 and 2015, we had record approvals, 10 and 11 in those two years. These products represent many different clinical indications and many different structures. Two-thirds of these products were important enough to get a more rapid review called a priority review, and 11 of them were considered orphan drugs. So, again, these products are growing in number and are of importance.

There are a lot of challenges to the review of these protein products. They’re made in a variety of cell

substrates. Each of these carries potential risks, viral risks, for example. They are not one structure; they are a mixture of many structures and may have variance in glycosylation, oxidation and PEGylation. Their high order structure really matters for signaling and may not always be visible from looking at the primary structure of the molecule.

There are manufacturing issues. These products can be very sensitive to how they are manufactured. Scale-up can impact the structure of the product. They can aggregate at various points in manufacturing which can have an impact on immunogenicity.

The mechanism of action is sometimes well understood -- receptor-like and binding and clear signaling -- sometimes not so clear -- and that really impacts the attributes that you need to look at for quality. And again, it's important to have very good bioassays to be able to assure the quality of these products.

Immunogenicity, as I mentioned before, is an issue. It can impact safety and efficacy. Whenever a manufacturing change happens, there needs to be a risk-based assessment of whether or not that change has impacted product attributes that are important to patients.

And there are a variety of issues with some of these products. The anti-infectives may be untestable in a

patient population; therefore, there's an animal rule. Some of these products are stockpiled, so a variety of other regulatory issues.

And, most recently, biosimilars -- This is an abbreviated pathway to approve biological products with a different set of evidence really relying on what the reference product has done clinically, and relating that by using analytical tools. Of note, I mentioned record years. This year, so far, I think at least six antibodies have been approved, one of which was the first biosimilar antibody approved in the United States.

With that, I am going to transition to Dr. Max to talk a little bit about our research program.

DR. MAX: I would like to explain how the research and the regulatory work that our office does work together. It has been likened to the warp and woof of a fabric, and the fabric of the OBP work product really relies on both research and regulation.

On the bottom half of this slide you can see several of the kinds of research programs that are ongoing in OBP. We have research into protein manufacturing science, into analytical methods, into mechanism of action, both of these intended actions of these biopharmaceuticals as well as drug resistance and toxicity which are important for their use and evaluation. As Steve mentioned,

immunogenicity is common with these products, and we also have to make sure that they are free of adventitious agents.

Finally, we have research on emergent problems, and this includes contamination, counterfeit and so forth.

We have in our staff a unique model, the researcher/reviewer model, where almost all of our staff are doing both research and regulatory work. The relationship, like the warp and woof that I mentioned, is shown here on this slide. Regulatory review of submissions that are sent by sponsors, also inspections and meetings, generate problems in review that are unanswerable with our current knowledge and require research, so we have the same folks involved in doing bench research that produces high-quality results that are mission-relevant and sometimes leads to guidance documents, certainly to publications in the scientific literature, and improves sponsor interaction and then feeds back on the regulatory decisions relative to these products.

The advantages of the researcher/reviewer model are that it provides specific knowledge to evaluate some of these issues like mechanism of action which impacts on potency assays, adverse events and drug-drug interactions, as well as it gives our staff hands-on technical experience with new methods that are being used by our sponsors. We

have state-of-the-art scientific knowledge that's being discovered relative to product development, analytical techniques and manufacturing methods.

I have diagrammed here the career paths that our staff go through. We have some temporary positions shown on the left and permanent positions on the right. Our staff members who are being reviewed in this site visit are both senior investigators. They have permanent positions and they are being reviewed for promotion.

I just want to outline the tasks that we gave to our visitors when they came for the site visit. They were to review the research accomplishments since the last review cycle and look at the research proposals for the next four years, looking specifically at novelty and originality, mission relevance, independence of the candidate from former mentors and their productivity. But this has to be taken in the context of their research support available from the office's various granting mechanisms and their time for research, which we aim for about 50 percent but in reality it's quite variable because we have no way of controlling the submissions and the timing of the work that comes in for the review side of things.

We welcome comments about the administrative or management aspects of the office. Regulatory activities

and regulatory work quality is not assessed by the site visit team.

Finally, I just want to echo our thanks to the site visit reviewers and the advisory committee for the time and expertise and suggestions to improve our research programs. This input is critical for fulfilling our regulatory mission.

DR. CRIPE: I have a question. Can you tell us what the regulatory burden has been over the last few years? Is it going up; is it something that's been fluctuating or been pretty steady?

DR. KOZLOWSKI: As I showed, the number of approvals has gone up. Proportional to that, there is a larger number of investigational new drug applications and submissions there. The workload is going up, and I think part of our reorganization into four divisions was trying to be able to better manage workload. It's not entirely dependent on the type of product. If antibodies go up a lot does that mean one group gets overwhelmed and another less so? So we want to be able to distribute the work evenly.

But there is no doubt that the work is going up, which is, in some sense, a very positive thing because it means biotechnology is being successful.

DR. WITTES: This is Janet Wittes. And your

staff, has that gone up commensurately, or not?

DR. KOZLOWSKI: We aim, as Dr. Max mentioned, at 50 percent. We're trying to set the way we assign work on average to give researchers about one-third of their time as regulatory work. That is a challenge to do with our workload. That is what we try and aim to do.

I think, again, we are expanding somewhat our full-time review groups so hopefully we will grow to help manage this, but I think it's always going to be a challenge balancing the workload as this increases. And we really don't know how much biosimilars will increase workload.

DR. ISACSON: Can you clarify what you said -- 50 percent was your goal?

DR. KOZLOWSKI: Right. Fifty percent is often where people are, and often principal investigators, as they are more senior, end up having a larger workload. But I think the long-term goal, considering the research staff, would be to have it around one-third. That doesn't mean that's what it is but that's what we would like to do, and that's how we're trying to assign and distribute work.

DR. CRIPE: Great. Shall we move on?

DR. MAX: We are on to Wendy Weinberg

DR. KOZLOWSKI: When I mentioned a third, what I mean by a third is targeting a third of the workload of

someone who does only full-time review. What percentage that actually works out to in terms of hours, that's a complex challenge to figure out.

Agenda Item: Research Program Summaries, Wendy Weinberg, PhD. Chief, Laboratory of Molecular Oncology

DR. WEINBERG: Wen Jin Wu is currently a senior investigator in the Laboratory of Molecular Oncology, and Dr. Wu's research program is focused on the family of receptor tyrosine kinases and downstream pathways in breast cancer progression, as well as looking at HER2-targeted therapies.

Specifically, his group has been investigating the roles of the erbB-2 member of this family and downstream Rho GTPases and Vps-34 in cancer progression. His group is also developing and optimizing therapeutic strategies for breast cancers that are resistant to trastuzumab and ado-trastuzumab emtansine, which are licensed antibody-based therapies that target HER2-positive cells.

In addition, his group has been elucidating mechanisms of toxicity that are induced by trastuzumab and ado-trastuzumab emtansine with the goal of enhancing the safety profiles for these antibody therapeutics. This research program then is critically relevant to the safety and efficacy of the oncology-targeted therapies.

This next slide is just a brief overview of Dr. Wu. Within the FDA community, he is currently a member of the Biological Research Coordinating Council, which is a group made up of -- it's a CDER and OBP committee. He has served as a member of the CDER Education Committee as well as its Vice Chair, and has been a mentor continuously for the NCI-FDA co-sponsored Interagency Oncology Task Force. In this capacity he mentors and oversees both the research and regulatory work of these fellows.

He has published. He is an author on 34 research and review articles and four book chapters, has received funding from both CDER intramural programs, the critical path program, as well as the Office of Women's Health, which is an FDA-based program. Based on his scientific achievements, he is currently the CDER nominee for the FDA Scientific Achievement Award for Excellence in Laboratory Science. This is currently pending.

His outside recognition is evidenced by his invitation to be speaker, including keynote speaker, at national and international meetings both for his research and regulatory expertise. He serves as an editorial board member for three journals, and as an *ad hoc* peer reviewer for multiple scientific journals, as well as research programs.

He is currently the President of the Society of

Chinese Bioscientists in America -- this is an elected office for this year -- and has served on the selection committee for the American Association for Cancer Research Charlotte Friend Memorial Lectureship.

In the last six months since the site visit, his group has published three primary research publications in well-established journals. He has received grant funding -- it's competitive funding from the FDA Office of Women's Health, and as part of this he has established a collaboration to investigate potential biomarkers for trastuzumab-induced cardiotoxicity. This is a collaboration with clinical investigators at Mass General. He has been an invited speaker at the 12th Annual PEGS Conference in Boston, has written a book chapter manuscript on trastuzumab-induced cardiotoxicity.

Within the lab, major research advances since January include establishing the technology in his lab for generation of biospecific antibodies, establishing TDM1-resistant breast cancer cell lines to support that project, and has presented his work at oncology rounds for the Office of Hematology and Oncology within CDER as part of the new Center for Oncology Excellence.

In the last six months, in terms of his regulatory contributions, he has been an invited speaker at the international meeting in Berlin to discuss antibody

drug conjugates and the regulatory perspective. He has led a team in the drafting of an internal regulatory policy document for our review of antibody drug conjugates. He is serving on a biomarker review team that is FDA-wide, and continues to perform primary product review for multiple new molecular entities from the pre-IND to the pre-BLA stage, and continues to mentor and oversee regulatory review by his lab members and signs off on their reviews as well.

That's it.

SPEAKER: Do you have any estimate of what percent of his effort is toward regulatory?

DR. WEINBERG: That's a really tough one. As Dr. Kozlowski said, we aim for a third, but I can tell you probably over the last month and a half it is, I would say, more like 80 -- it has really been a very large portion.

In addition to his own primary review he has been training his lab members. There was some turnover in his lab with the reorganization, so he has a couple new reviewers in his lab and his staff fellows are new, so he has been bringing them up to speed as well, and they have been gaining their own regulatory load. So it has been quite busy the last number of months.

Agenda Item: Research Program Summary, Serge Beaucage, PhD, Chef, Laboratory of Biological Chemistry

DR. BEAUCAGE: I will begin. At the time of Dr. Baolin Zhang's site visit, his research program entailed four areas of research, and those are the following. The identification of biomarkers for predicting tumor response to a new class of protein targets targeting death receptors including TNFR1, Fas, DR4 and DR5.

He also tackled the development of methods for profiling glycosylation variants in therapeutic proteins; the development of methods for the detection of biological toxins such as ricin and Abrin in environmental samples; and investigation of the aggregation of therapeutic monoclonal antibodies in human plasma.

Now he is pursuing investigation of the mechanisms of action of anticancer drugs and the pathways leading to tumor resistance to those drugs. This includes an understanding of how protein modifications, especially glycosylation and aggregation, affect the safety and efficacy of therapeutic proteins.

The specific aims of the research projects entail identification of predictive biomarkers of drug-induced cardiotoxicity; molecular profiling of circulating tumor cells towards predictive cancer biomarkers; the unraveling of mechanisms whereby cancer cells resist death receptor targeted therapy; the development of methods for detection of ricin toxin in environmental samples; the development

and improvement of methods for glycan profiling of therapeutic proteins; and ways to assess modifications of therapeutic proteins in human plasma.

Since the last visit, Dr. Zhang has published three papers -- two research articles that were related to glycan analysis and they were both recently published in the journal, mAbs. And the book chapter was written for the detection of apoptosis.

He has many manuscripts in preparation. Four of these manuscripts relate to death receptors and apoptosis, and there is an invited review that is dedicated to targeted cancer therapy.

Dr. Zhang is also very active at giving presentations at local meetings and national and international conferences. He has been the invited speaker at the Markets and Markets Conferences on Biomarkers in San Diego. He was also an invited speaker at the Biotherapeutics Analytical Summit in Washington, D.C. He was also a session chair in that conference.

He gave a few talks here at the FDA, and he presented, very importantly, at the Gordon Research Conference on Cell Death in Spain, and at the Gordon Research Conference on Personalized Medicine in Hong Kong earlier this month.

Dr. Zhang has submitted grant proposals, one for

the Fiscal Year 2017 Chief Scientist Grant -- Predicting cardiotoxicity of oncology drugs in individual patients, and one for the Office of Women Health -- Identifying molecular signatures of circulating tumor cells to improve breast cancer therapy.

In terms of regulatory work, Dr. Zhang continues working as a primary reviewer for novel biotechnology products submitted as INDs and BLAs. These also include original pre-INDs, annual reports and IND amendments and BLA supplements.

Since earlier this year, Dr. Zhang also works as a secondary reviewer with the responsibility of overseeing a review team consisting of three primary reviewers.

Currently, he is also under FDA special assignments. He is the Vice Chair of the FDA/CDER Regulatory Science & Review Committee, and he is also a member of the FDA/CDER Biomarker Qualification Team.

There are also many other things that I didn’t put on slides because I thought I was exceeding the time. He has been the lead reviewer on several scientific journals. He is on the editorial board of nine scientific journals. That’s it, thank you.

DR. CRIPE: My only question is when does he have time to sleep?

DR. BEAUCAGE: This is a question that we should

ask him, but as far as I see, I don’t see him that often. He is buried in his office, for sure, and working really hard.

DR. KIM: Are there any other questions? If not, I would appreciate if people on the phone could identify themselves so we can take the roll.

DR. ROSE: Steve Rose.

DR. WITTES: Janet Wittes.

DR. BOLLARD: Catherine Bollard.

DR. BARTLETT: This is David Bartlett.

DR. ANDO: Dale Ando.

DR. PLUHAR: Grace Pluhar.

DR. ISACSON: Ole Isacson.

DR. EMENS: Leisha Emens.

DR. ZOVEIN: Ann Zovein.

DR. CRIPE: Tim Cripe.

Are we missing anyone?

DR. KIM: Dr. Bartlett?

DR. BARTLETT: Yes.

DR. KIM: Dr. Bugbee?

(No response)

DR. KIM: Dr. Byrne?

(No response)

DR. KIM: Dr. Zovein?

DR. ZOVEIN: Here.

DR. KIM: Dr. Stegemann?

DR. STEGEMANN: Here.

DR. KIM: Dr. Emens is on the phone. So that is everybody.

DR. CRIPE: So that is the end of the formal presentations and now we go to the open public hearing session.

Agenda Item: Open Public Hearing

DR. CRIPE: As far as I know, we don't have anyone registered to speak, but if anybody wants to come forward they are allowed to do so now.

(No response.)

Is there no one in the room?

DR. KIM: No, there is no one in the room, so we can adjourn the meeting.

DR. CRIPE: All right. We will adjourn the open session and begin the closed session.

DR. KIM: This will be the end of the open session. Those of you who are not participating in the closed session meeting, if you could vacate the room we would appreciate that so we can set up for this next session.

(The open session was adjourned at 1:47 p.m.)