Lauren Milligan: Alright, good morning, everyone. Let's get started. First of all, thank you. To everyone who traveled far and wide. We have some pretty incredible businesses and people will come for today's workshop. So thank you very much. We're going to be having quite an online presence today, probably close to 900 people logging on. So welcome. My name is Lauren Milligan. I'm from the Office of Clinical Pharmacology here at Senior FDA. I think we're all good and […]. So it's my pleasure to wish you well and meet you in today's workshop. Developmental Best Practices and Physiologically Based Pharmacogenetics Modeling to Support Clinical Pharmacology Regulatory Decision Making. We look forward to robust discussions on all aspects of today's workshop. So we have, all the sessions have time allotted for questions and answers. We will talk to accommodate as many folks as possible at the microphones, and when you ask the question, please state your name and affiliation. So without further ado, we're going to have our opening remarks by Dr. Peter Stein and Dr. Christopher Joneckis. Dr. Peter Stein is our first speaker. He is the director of CDER Office, Deputy Director of the Office CDER Offices New Drug. Dr. Stein has more than 30 years of academic, clinical and industry experience including Vice President […] Metabolism Development and Jansen, Vice President for Late Stage Development Diabetes and Technology at Merck Research Laboratories, and in FDA in 2016 as our new Deputy Director.

Peter Stein: Well, thanks. Good morning and welcome. I have a disclosure, I actually have a slide for this. I am not a pharmacologist. I'm a clinician, and I had to look up PBPK. You know, I've been reading about it for 20 years, I probably couldn't tell you the abbreviation until I looked it up this morning. So now I do know what it means. But what I'm going to talk about is, is more broadly, the role that I think that innovative therapy, innovative approaches like PBPK in play in our, in our drug development enterprise because there are and have been many changes in drug development and in, and in the regulatory landscape over the past decade to the tape recording to recognize and I think they just elevate the importance of the way that we develop drugs, the importance of efficiency and drug development, and I think that these are innovative therapies. Innovative approaches are incredibly important to enhance for our understanding of all the drugs that are increasingly complex, and also to prove the way that we develop drugs to be more efficient. I think PBPK is a great example. It does offer us the opportunity to develop models that can answer a range of important questions, […] drug interactions, on drug dosing, on drug disease interactions, and other such important questions in development, potentially both more accurately and more efficiently. So as I've mentioned, the development landscape is changing. And I think a few comments about what those changes are, may be relevant. We've been seeing over the past decade shift from a focus on large

common chronic diseases like hike in diabetes, […] in asthma, towards more focus on rare disease and diseases such as in and late stage of resistant disease. I look back about, I look back a few months ago to look at a suitable portion of any means that are focused on common diseases versus real disease and it's gone from about 15 or so percent of our drugs targeting a rare diseases or molecular stereotypes to tripling that and about half as many focused on common chronic diseases. So we'll shift from large population targeted diseases to more rare and small population targeted diseases driven by many factors, both financial, physical issues, but certainly abounding science for better understanding and look at the drivers of genetics and genomics as disease. Recognition biomarkers is stored as disease subtypes. Obviously, also the neutral platforms we approve the first SIR […] as those in the whole range of the biological platforms that are that are in development where they are now approved. We're seeing also changing expectations edging expectations of patients and they're more involved in drug development, both in terms of identifying appropriate disease targets, providing input on the study design, contributing to our consideration of the benefit risks of drugs. We're also seeing expectations and data sources will be involved in drug development from the implementation of health technology, in digital biomarkers to the use of real world data and no evidence to inform regulatory decision making, expanding labeling. Of course, there's also a focus on costs and if it doesn't, isn't involved in drug pricing, but we we will comment assets, and that can be impacted both by a focus on generic development or involving similar programs, but also in working with developers to make development more efficient. Obviously, that's an important role that we can play in, in trying to address the issue of costs. And with all the changes that have occurred, one thing that hasn't occurred is really change the efficiency of growth development, if you look back over the last 10 or 15 years, about 10% to 11% of drugs, they're integrated development are ultimately approved, which is the FDA approval, and it hasn't really been changing very much, a little different for small molecules versus large molecules, but overall, the efficiency of drug development hasn't changed. And certainly things that we can do to improve that efficiency will, of course, the important in terms of the overall cost of the enterprise. So these changes in other cases mean that we do have to make efforts to try to make the drug development more efficient. But the one thing we have to also do is make sure that our standards for assuring the safety and effectiveness of the drugs isn't compromised. And we have a number of programs for that. Of course TV is one of the ways that we can do this in the context of model modeling for drug development, complex innovative designs, or biomarker qualification programs are focused on […] evidence and our patient focused drug development programs to try to introduce new and innovative ways to think about drug

development, hopefully improving efficiency as well as the quality of the of the reviews that we can do. This brings us back to today's workshop. As I said, TV became offers, on potential way to enhance efficiency and development, but also increase our understanding of the drug that we are developing. I think it's particularly important. If it's PBPK enhances our mechanistic understanding of how a drug is handled, how it is absorbed and distributed, the appropriate dose range, how its impacted by disease and organ dysfunction, how it reaches and engages its target, and its interaction with other groups, among other important considerations. I mentioned the importance of efficiency and one approach of course is using new innovative tools such as PBPK to focus development resources, answering questions, such as potential for drug interactions, without the need for additional clinical studies, and of course it requires us to really understand this tool, you know where and how to invest the implemented. But another important approach to enhancing efficiency is for total harmonization. PBPK is a program as an interest both to us and to other regulatory agencies, but the most consensus as to how when this is best implemented, it doesn't necessarily improve efficiency when programs require a study in one region but not another region that's not necessarily improving efficiency, so finding ways to be across different regulatory agencies can embrace common approaches to the implementation of innovative technologies is of course greatly important, and I can assure that we do have discussions with our regulatory colleagues across the ocean and around the world to try to come to common understandings both that programs and that innovative tools and methods. So there is some real opportunities here and yet there also are many challenges, and I think today's workshop is going to be a great way to take a step forward to helping us and to understand the role of PBPK can play and to improve it forward. It is an implementation interactive element in our ability to understand how and where drugs can be used. So I want to thank you for attending today or for calling in today's meeting and thank you very muchyou're your attention.

Lauren Milligan: Okay, next please welcome Dr. Christopher Joneckis, Associate Director for New Management at CDER, here at FDA. Dr. Joneckis is the senior lead for user negotiations and is responsible for the development and oversight of data and review standards, information technology and regulatory business operation.

Christopher Joneckis: Good morning everybody here in […]. Unlike Peter to really looked it up, I'm actually a pharmacologist by training. I graduated degrees in pharmacology. I had a PA of course a long time ago back in graduate school, and before that, I was actually doing a lot of development at NCI so I probably had a better understanding of classical PBPK. […] there. The challenge as Peter mentioned are

across the board and for biologics as well. We have in the last six years 75%, approximately 75% of the products that we have approved more […] drug products, and some of those are extremely small, well under the 200,000 patients, but all that is used to define the classic product. Now, some additional challenges for a lot of the super biologics that we have. They're very complex these days, they were ones that we regulate. For example, some of them were […] cell therapy, you may have cells those isolated from a patient that manipulated give gene therapy type. The therapist expressing proteins on the surface. There's a lot of characteristics. There's a lot of variability starting with the inherent variability in the patient cells, for example. That high degree of variability and actually process makes it even more challenging in many cases to predict that response to the patient and what we're gonna see in the actual patients and their response to the all the variable is manufacturing, starting again with the patient cells, and all the manipulations that happen. We have a large variety of rapidly evolving technical and scientific issues that address the safety, potency, and efficacy of new biological products that really require a lot of knowledge and understanding the basic and applied research to address those problems. We have seen at CBER a trend to have an increase in the use of traditional quantitative PBPK, things such as population monitor kinetics, exposure response monitoring for our plasma-derived recombinant products, and we actually have seen some interesting luminary applications of this field, some of our vaccines and gene therapy. We encourage those kinds of explorations as discussions on some types of modeling, whether it be an informal pilot that we have had since the beginning of the different states or an individual applications that companies would be submitting. I think we've made a lot of strides CBER and FDA in advancing for quantitative science. For example, we have a very good collaborative project with NCTR or National Center for Toxicological Research and looking at monitored approaches to toxicology for aggravated plasma vaccines. We're also looking at innovative clinical and evaluation personalized medicine to improve product development and patient outcomes of things such as individualized dosing for some of our biologics is extremely relevant, and your personalized medicine can be bought at this pump pulling off the right drug off the shelf and administering this patients perhaps based on genetic profile, genotype or phenotype, we're really now starting to think about the individualized medicines, that really means creating the right drug for the patient for very, very small subsets of populations as patients, and that's going to provide, I think, some interesting challenges as well for how various types of large populations can be potentially extrapolated to various types of individualized issues. So I think everyone knows as part of the PDUFA VI, we the agency launched a model-important drug development initiative and that resulted in several things including the

topics that we're going to see happening here today. There was a very good collab, there was a very good collaborative model and stimulated information management work, working group that goes back and forth from drug development to discuss a lot of the applications to make sure what the knowledge back and forth and we're very committed to a series of these workshops to identify best practices and […] forward, I believe from looking at the slides that I saw today there's going to be a large variety of different approaches, especially a lot of the physiologically based pharmacokinetic modeling. We are at the early stages of applying a lot of that in secret. So great thanks to all the speakers and participants, especially I'm thankful to the organizers. The […] at CBER and corollary groups in CDER and of course all the participants from the FDA, academic and industry speakers, I think it's gonna be very interesting and quite a useful. Thanks.

Lauren Milligan: Okay, thank you both for your introductory remarks. We're going to start off session one […] through 60, […]. I'm pleased to introduce as moderator for session one Dr. Issam Zineh, Director of the Office of Clinical Pharmacology at CDER FDA. Dr. Zineh is a recognized expert in the fields of drug development, evaluating clinical pharmacology and precision medicine and currently staff of over 240 to enhance drug development through clinical pharmacology.

Issam Zineh: Thank you very much, Lauren. I want to take this moment to acknowledge all the […] done, as well as the staff really throughout multiple centers of FDA, putting this together, you can tell by the agenda. It's about, really significant amount of effort that's gone into these speakers, the moderators, the staff, in CDER, […]. Thank you very much to all the participants and I think this is a very exciting time for all of the, for drug development, and you can tell that in some sense by the number of registrants that we have for PBPK workshop, nearing 1000 and virtually in several hundred in the house. So thank you for all the, to all the attendees as well. So I just want to […], my remarks three and four […], what we think is the importance of this workshop and these kinds of workshops in terms of stimulating […] and sciences and quantitative clinical pharmacology. […]. It's been an exciting year and a half for modeling for drug development in this. Dr. Joneckis mentioned under the prescription drug user feedback. We've had several enhancements to our science and the way we do regulatory business within multiple centers as it relates to modeling for drug development. It's been long recognized that MIDD is an enabling or can be an enabling approach to dealing with some of the efficiency issues in drug development as well as lowering some of the regulatory uncertainties and decision making and it's really been decades as the work in terms of bringing this to the mainstream. Under a PDUFA VI, we have several enhancements including raising, increase the scientific capacity to deal with modeling contract development, both in terms of increasing staff numbers but also educational initiatives. We have committed to revising or developing new policies around modeling for drug development approaches and we've committed to the series of workshops. And we feel as though the workshops in particular are the catalyst to modernize to some of our thinking and also to advancing the educational initiatives. What we've learned over the past year and a half or so under the MIT program should come as no surprise to the crowd here in terms of what we think are the requirements for advancing some of these approaches, and they include creating an environment where stakeholders are receptive to these kinds of approaches, in […], and quantitative approaches, having interdisciplinary collaboration as well as really pushing the issue around evidentiary standards and frameworks and requirements. I think this workshop will go a very long way to address some of those issues. As I mentioned, MIDD is happening all over the agency. It's happening in multiple areas within CDER. It's happening in the Center for Devices as well as Center for Biologics, and many of the staff here are representing a lot of that significant work that has been going on over the years. Additionally, there's been in recent, I would say within the last year or so, a call for harmonization approaches so that when dealing with regulatory agencies across the globe, you can have some predictability and some consistency and how regulators view and apply

quantitative approaches, including urges and so we feel as though this workshop again will advance the dialogue there. So, to set the stage we have a very exciting first session. I'm pleased to open this session and introduce Don Mager. We will just by way of housekeeping, I think what we'll do is we'll have all three talks. We have Don Mager presenting with you from Academia Research. We Steve Hall talking about some of the work of the IQ consortium and providing industry perspective and Dr. Yaning Wang talking about PBPK within the regulatory context of these. These will be 20 minute talks. Please take note of your questions, because as soon as all three talks are completed, we'll invite you to the microphone to ask your questions, and I will also ask questions if no one has any, but we're hoping that there will be a very dynamic engagement from before so please, please come to the, to the podium. So with […] introduction, it's a pleasure to introduce Dr. Don Mager. He is Professor and Chair of Pharmaceutical Sciences at SUNY, Buffalo. He's also President and CEO with Enhanced Pharmacodynamics. He has served in terms of FDA services served on our Pharmaceutical Sciences and Clinical Pharmacology Advisory Committee, and he currently serves as associate editor and assistant editor at CP PSP. He's a Fellow and former President of the International Society of Pharmacometrics and is a Fellow in the President-Elect of the American College of Clinical Pharmacology. He's a renowned researcher, of course, I'm sure many in the crowd are very familiar with Don's work and a leader in the field of quantitative and systems pharmacology, Dr. Mager.

Don Mager: Well, good morning everyone. Thank you, Issam, for that wonderful introduction. It's really a great pleasure to be back here at the FDA. Looking forward to a really exciting day. I think the lineup looks very exciting and looking forward to the discussion throughout the day. I'd also like to thank the organizers for giving me the opportunity to present here and for all the help in putting this all together. So, my goal today, I really wanted to bring a focus to the biologics. I know, we've been talking quite a bit about PPBK for small molecule. So in addition to getting some academic perspective here, I also wanted to raise awareness of some of the state of the Science for Biologics in the process. So I thought we'd start with just taking a look back first, you know, in the past five to seven years where the focus had been in PBPK, and you know, if you go back to publications in the past, you know, we certainly were talking quite a bit about validation. And I'm really looking forward to the discussion today to know more about validation and what is going to be considered appropriate for validating a model. I think that's, even though we're talking about seven years ago, it is an incredible hot topic today as well. And so we're going to talk quite a bit about that today, I think, but to what extent should the model be considered adequate? What are the competence measures, but the adequacy of the model and all that really starts with a clear statement of goals and objectives of what you wish to achieve? And I

look forward to discussing that more. There was also a lot of focus on the essential content, but what should be submitted for consideration for clinical pharma view, and I couldn't agree with the first bullet more, it's really you have to have a clear statement of goals and objectives that often gives you a sense of the types of the models that you're going to consider, if it will little go towards what you're going to consider as validation into, instill confidence in answering that particular question that you have in mind. Workflows, verification of software, all critically important. The inputs parameters, software information, and the details of, the clear details of the experimental simulations that are being done, as well as sensitivity analyses. I also appreciate the last bullet and question-oriented evaluation and assessment of results asking very clear questions and there's a couple of examples show here from the publication from collaborators here at the FDA. You know, […] simulation to predict the magnitude of DDI, etc. I think we have a clear statement of goals and objectives and then clear questions to ask. […] I'm finished, everybody really achieved what I had set out to achieve. I think if you're thinking about the scientific challenges, again, my goal in this talk was to raise some scientific challenges, focus on biologics and hopefully give a framework where we might go in the future. As I said, validation is still I think the main point that has to be considered and how we'll know whether model is adequate. I think the integration of omits data is still a clear challenge from all different platforms, genomics, proteomics, etc, and how that information is going to be effectively integrated into the analysis, increasing detail of subordinate levels. We recognize that many of these tissues are heterogeneous, and will instead of having just simple big boxes, that's a brain or heart, we're going to want to be much more specific and have a much greater granularity as to where these drugs are going. Refinement of models, system parameters for special population is going to be critical. We've seen a lot of development in that area, integration of the micro physiological systems that's showing great promise and not only understand the predicting disposition, but also having a sense of interest having variability coming from some of these micro-physiological systems, and my focus today is going to be really talking about biological therapeutics and some of the complexities and how we might move forward there. And I think the take home point I'd like to make for this talk is the last part, the need for collaborations to enable decision making. I think when you start talking about PBPK for biologics, make the lines between PK and PD probably dynamics are not as clear, right? For small molecule, we're almost always focused on a disposition of the small molecule drug. But for biologics, you oftentimes can't separate PK from PD because the action of the compound is feeding back and having an influence on the disposition of the biologic and the ultimate efficacy of the compound, both safety and efficacy. So I think this is really going to usher in a new wave of QSP, Quantitative Systems Pharmacology coupled with PBPK because of the need for that interaction between the dynamics of the compound as well as the disposition of the compound. So, I'm going to focus on some of the complexities of biologics. This table just

simply highlighted some of those differences between small molecule and large molecule. I'll highlight just the clear ones, to essentially being FCR and trafficking, which allows for the one-half lies target media that disposition were binding to the receptor influences the disposition of the content. That's something quite unique for Biologics, only a handful of small molecule drugs tend to show this behavior, and then of course, immunogenicity, another big component that separates small molecule from large molecule. Again, some of the important features we want to keep in mind. We've had over the years the development of several really useful PBPK models for biologics, this comes from Joe Balthasar's lab, and each tissue on the lab is broken up into several compartments. You can see in the top right, all of the major processes that govern the disposition of monoclonal antibodies, for example, […] convection into the tissue, you have binding temp CRN and you have FCR and trafficking and the salvage pathway that protects IGG from degradation. You have clearance of the free-drug, and then at the bottom, you see the additional complexity of buying into the target, and that target and having the opportunity to influence the disposition of the molecule. These types of models then been built up over the years. This is a platform model from […], and it's built upon quite a bit of data that have been in return for a number of different, in a number of ways. So for example, in the mouse, you have a number of different experimental subtypes that include FCR knocked out animals or animals that have been challenged with nonspecific IGG in order to perturb the system, but plenty of dose-dependent data of course, across VCs and the model is shown quite useful describing the time course of exposure not only in plasma but in tissues of interest. The models have shown predictive ability to be able to anticipate the pharmacokinetics in humans for biologics, not just a linear clearance, but also dose-dependent clearances. If you have some solid information about the biology, in terms of where the targets being expressed, how much and how rapidly it's being turned over, in many cases, you can anticipate whether you're going to see a nonlinear distribution and elimination of the compound and these are now readily predicted from these PBPK systems. You can see the complexity growing quite a bit over the years. This particular model is for a catch and release antibody for anti- PCSK9. This is the idea of buying into a lie in bringing it into cellularly and then releasing it based upon PH dependent and binding. This is an added complexity of a pH-dependent binding to the line, and this is meant to sort of catch to the target delivered to the tissue where it could subsequently be degraded and so as to speed of the process of removal of whatever it is that you're targeting. So I get the questions quite often when I showed this slide, do I need that level of complexity? If I'm trying to describe my particular molecule, and in some cases, it's not needed to describe perhaps just a time of course of exposure, but again, it goes to the goals and objectives of the analysis. Something you can do with this model that you can't do with some of the standard models is actually begin to look at the pilot physical properties of the molecule and asks, is there an opportunity for improving upon the disposition and dynamics

of the compound. So for example, with this model, you're able to look at different properties such as the disassociation, a pH 6 and the binding at 7.4 and see its ultimate effect on the clearance, and so why the company if you're getting in developing this particular molecule, you may have a sense of whether there's further opportunity to optimize the design of your molecule, or whether or not you've achieved a certain space where there is no further advancement by modifying the binding of the compound. So again, it goes to the goals and objectives and they can't be, you know stated more importantly, that has to be stated upfront. PBPK for Biologics has been coupled with population-based algorithms both in the terms for estimation, but then also projection in this study for Trastuzumab, and not only are we capturing the central tendencies here, but the authors were able to actually anticipate the degree of variability in the design here as well. So the model is able to recapitulate not just central tendencies, but also the degree of variability within this particular study. We can also couple this with estimation procedures, if certain parameters need to be fine tune or we can couple them with population-based modeling with PBPK approaches. The models have been used to explore other important components and this is a PBPK model for Antibody-Drug Conjugates. This comes from a Great Thurber Lab in Michigan. The model is shown the left. An interesting feature is the binding site barrier and what they were nicely able to show is that if you gave an upfront dose of cold Trastuzumab, then added your ADC, you got much greater distribution throughout the tumor. So when you don't give a prior dose of Trastuzumab, most of the Antibody-Drug Conjugates sits right within the vascular accessible spaces. But when you give the cold Trastuzumab and block some of the receptors, you'll begin to see greater and greater distribution. This had an improvement and efficacy of the compound. And so again, this is an important insights and how this molecule is distributing and also causing its pharmacological effect. PBPK has been useful for drug-drug interactions. Of course, that's the main stage so far in small molecule but also for large molecule. We know that there are a number of cytokines that can influence the metabolism of small molecule drugs, and so there is an opportunity here for drug-drug interactions. This is just one example where this particular monoclonal antibody targets aisle 6, and aisle 6 is one of those cytokines that, it does have an influence on the metabolism of small molecule. And in this study they were able to reasonably project that interaction from the PBPK model. As they said, we're going to have increasing granularity in these models. We're not just going to have one box that says brain. We're going to need to have much more granularity and you see here we have broken down, this comes from […] Lab in Buffalo, where they've developed a translational PBPK model from IGG antibodies in the brain, and you see the different regions of the brain that broken up into the, into the spaces. So it's not just brain as a whole but exactly which reaches within the burning. And in perhaps this is going to be incredibly important as we targeted very specific areas for certain diseases. The data we're building, I'm just showing you a couple of

profiles here in monkey, both in plasma and UCSF, but the model was built up across several species, including some data from humans. I think another important area is going to be the mechanistic modeling of subcutaneous absorption. I think this is still a very active area. We'll still have a challenge in reliably predicting the extent and rate of absorption of monoclonal antibodies. There's some complexities there that we still don't know. This is an early model comes from […] that has a subcutaneous absorption of therapeutic proteins in a very general way. But you know, it's a very simple model and I think more of a mechanism needs to be built into that. We and others have shown that the disposition of monoclonal antibodies after injection is at least in the smaller species can be quite complex. It was showing for rituximab, that a low dose gives you a bio availability about 70%. But then in high dose, it will drop down to 31%. So we see this non linearity that we don't see doses in humans. And so really understanding those complexities may help us to better project the extent and rate of absorption in humans if we had a mathematical model that bridges the gap between species and so more work should be done there. We're not the only group, but obviously there have been others that have shown this where you have injection of the subacute dose, you have quite a bit lymphatic uptake. Here in this particular paper for Monash, we see a lot more of the details measures such as the recovery in the lymphatic space. We see this nonlinear uptake, which we have attributed and others have attributed to FCRN at the site of injection. And so we see a number of these complexities and I think we should have a better sense of that would allow us to look more reliably predict the extended rate of absorption in humans, but also the impact of adjuncts such as how the remedies or other elements that may enhance absorption from the second use case also is be trying to understand immunogenicity, having a more mechanistic model subcutaneous absorption maybe an important component. I'm going to skip this in the interest of time, but essentially we can through simulation explore the role of the capacity and affinity for transport processes. We also know that some of the system components scale nicely across species including lymphatic flow rates. And so there's an opportunity here to build more mechanistic models of drug absorption. As we move into bi-specifics and immunotherapy, it was noted already this morning, these are much more complex molecules, and much more is going to need to be understood. For this this particular dark, this is a bi-specific construct that is targeting T cells and CD123. This is a compartmental model that we published last year, and essentially, I feel we're going to need to include circulating and tissue associated immune cells […] in our PBPK models. This is starting to come out. I know many folks and industry are already doing this, and we need to have I think more of that. And this is where again, there's this blurb between PK and PD, where we want to know not just the disposition of the molecule, but the disposition of the cells of interest. For example, the CD3 and then not just how many cells are present in a particular tissue, but whether or not they're active or quiescent. So the dynamics are going to be important in understanding disposition and safety and

efficacy of these molecules. So you're seeing more of these compartmental models being developed and I think we have an opportunity here to add that into our PBPK framework. This further extends that this is a very nice translational model that comes from the folks at Merck for a checkpoint inhibitor. This was a translational model and called semi-mechanistic driven by receptor occupancy. But again, I think more mechanistic models are going to be needed to include effective cell dynamics and potential for drug-drug interactions, both benefit, here I'm talking about beneficial drug-drug interactions, agilent therapies. So again, other molecules that may alter the particular cells of interest, or the number of receptors per cell could have an influence on the disposition of the biologic, but also had an influence on the dynamics of the molecule as well. And again, as we get into cell based therapies, I think PBPK again, can have a meaningful role here. So far, we've seen relatively simple compartmental models in describing cell-based therapies. We see, of course, when you're giving […] T cell, you have this expansion phase, and we have a clear sense of what's going on here, but the dynamics and and the kinetics and dynamics seem to change per product. I think, again, a PBPK approach would be incredibly useful here to not only understand numbers of cells, but activity of cells as well. How many cells are getting into a particular tumor? How many, and whether or not those cells are active at the site of action. We have a host now of antibody-based construct. This is just a small sample of the different constructs that are becoming available. Where I think we need to move forward is a more complete and unified PBPK model for biologics, just as we have for small molecules. Where we have built into our small molecule models, our drug properties, right F cRn Affinity, protein binding, in-vitro metabolism. We need to begin to put in bi-physical properties of these molecules in for biologics as well so that we can understand the time and course of exposure across them. So, we're not building a new model for each and every antibody-based construct. So, we have, we know some properties. This comes from Donald Shaw's lab looking at the role of size in the clearance of a tool box set of compounds we can see you know, molecular weight here is what was the radius and you can see what the relationship looks like for this tool box set of compounds, but in contrast to QSAR, I think we need to move to integrate the biophysical properties so that multiple pathways can be built in to a general platform model for understanding the kinetics of diverse anti-body based constructs, and just to drive that point home, this is where it comes from managing, looking at the use of cryo preserved hepatocytes in characterizing the clearance of antibody-fusion, protein consciousness. And so this is really excited, again, using an in vivo vital asset to inform the in […] properties of the molecule, something that we do quite a bit for, for small molecule drugs, quite a bit less of in biologics. And so they were able to show that the clearance of the compound could be broken down by a number of factors including F cRn Affinity as well as a hepatocytes assays as well as […] as well as in charge here. But the charge here is again, just the classic bulk charge. And I think we need to move beyond that

and start to think about the electronic distribution across the molecule chip and patches that can be calculated and built into physiological models. So I think this is where we're headed. We need to be using more of the biophysical the properties in just as we already do for small molecule drugs. So I'm going to stop here. Again, I hope I raised some awareness. First of all, a strong need for risk informed credibility assessments, which I think is going to be a big topic of today. I hope I've shown you some of the complexities of biologics and in pointing to where I think the science is moving. Most importantly, we're really talking here about interdisciplinary collaborations that are going to be needed, and I think this will usher in a new framework of QSP PBPK models for biologics, which are going to be incredibly useful in drug discovery and development. And as I've mentioned at the last point, I think we need more biophysical measures built into that as well. So thank you for your attention. I'm looking forward to the discussion today. Thank you.

Issam Zineh: Our next speaker is Dr. Steven Hall. Dr. Hall is Senior Research Fellow, of the Drug Disposition Department in Eli Lilly and Co. and has been in this role for over a decade and part of his responsibilities have been for developing new quantitative preclinical and translational models. He's also led several EPK initiatives in the translational and adding leadership group of the IQ Consortium. Prior to his role at Lily, Dr. Hall is Professor of Medicine of Endo-Pharmacology and Toxicology at the Indiana University School of Medicine and Associate Director of the Division of Clinical Pharmacology at the NIH Supported Clinical Pharmacology Training Program. He is a past board member, past chairman and member of the board of the Pharmacokinetics and Drug Metabolism Section of the ASCPT, and has served on several NIH study sections. Dr. Hall is incredibly well published with over 200 peer reviewed articles in the fields of pharmacokinetics genetics, drug metabolism and drug-drug interactions.

Steve Hall: Thank you, Issam, for that introduction and thanks to the organizers for giving me the opportunity to come and present here today. I can show you some data that comes from Eli Lilly and Co. I'm also going to show you some data that comes from the IQ consortium or to give it its full name the international consortium for innovation and quality in pharmacy development and we see what we call it the IQ consortium.I'd like to acknowledge some of the help that I received from the current PBPK working group, this time of the translation and leadership within the IQ consortium, and I think IQ is uniquely placed to really facilitate the development the PBPK […]. It provides an umbrella organization in which pharmaceutical companies can get together to discuss ideas of mutual interest, exchange information in a non-competitive way. And thus, to help solve some of the big questions around data that we need for validation of models and I hope that it will become a little clearer as we move forward and I think today there are more than 30 of the larger pharmaceutical companies all over the world that are currently part of this effort. So within the pharmaceutical industry, then PBPK modeling is used across the entire continuum from discovery to development. In the early phases of development, we're using it to help understand the potential drug ability of the molecules as we move them into building clinical development. The PBPK models is highly influential in determining the clinical pharmacology program and to enhance its efficiency and ultimately is increasingly solutions and in labeling of drugs. This is sort of a continuous learning confirming paradigm in which PBPK models essentially represent hypotheses which are tested every time new clinical information becomes available.So in discovery, we generally accumulate lots of […] data and physical chemical data. You can see on the left-hand side, and we use along with multi-property scoring systems to triage large number of tables, some of which then make it into preclinical models where we obtain data that data. That PK data can then be used to test whether

we have a reasonable correlation between our in-vitro measurements and in vivo connection. So this in-vitro to in vivo extrapolation or idea as it's generally referred to, is often used then to give us confidence that in-vitro data that we're producing would result in a reasonable prediction of the human pharmacokinetics of these new drugs. This together with pharmacodynamic information can allow us to look at whether we really think we have the drug […] or not and this cycle obviously goes around many times before appropriate drugs are then covered. So that the IVIVE process shown here in a little bit more detail. Here's an example of one of our data sets and we will determine the in-vitro intrinsic clearance of a model, a series of molecules in dogs and mice. We got that in the microsomes. They are on the left and the hepatocytes on the right. And you can see that there's a reasonably good correlation here for the hepatocytes data suggesting that we would have some competence in the prediction of our human data […] use this as our as our screening system. But I think importantly, there does seem to be some confusion here. This is not the sort of data we will be submitting in a package for drug […]. This is truly a tool that we use in the discovery process clearing the uncertainty in the IVIVE process is considerable. And so it's not something that we will be taking forward into the ultimate description of the molecules. So what did we actually submit and I thought I would use case example with […] from some of our vocabulary to illustrate this. So the Abemaciclib, these are relatively recently approved CDK4 and 6 inhibitor approved for the treatment of HR-positive, HER2 negative metastatic breast cancer is extensively metabolized by the sick three and four at times. See there, that this produces a couple of oxidative metabolites including the M2 metabolites, the M20 metabolite, both of which are active and the M2 metabolite is clearly […] to the METU […], which again, is an active metabolite. So, there was likely a […] was completely metabolized to by step three and four and then these active metabolites are further processed by […]. So, this is the drug that has a relatively low clearance and bio availability is at least the absorption from the test to lose high the FG is recently high and the FH to of course […] assistance the clearance. So, because we have these active metabolites, the Abemaciclib, we decided to use an additional metric of exposure which is to combine the area under the curve of each of these active metabolites and do that in a way that corrects the differences in potency and fraction unbound. So, we basically have the, the potency correctly unbound, active species to correct for finding correct potency. And so for example, after a given intervention, we have an AUC ratio, which would be the sum of these the AUCs after the invention over that control. And the rationale for this is quite clear here in this table showing that in-vitro, the potency of parent and metabolites towards the talk is quite similar, and the fraction unbound is quite similar. From the […], we know that easy to calculate

certainly significant concentrations impact accounting for almost half of the certainly radioactivity that was observed in plasma. So we have this reliving remodel another website with which describes this elimination pathways through security and we have fractions metabolized based on the next balance study, based on an absolute by availability study, and using the in-vitro data that we've accumulated. But at this point, we really don't have the confidence in molecule that would lead us to actually predict drug interactions. So at this point, we go ahead and run some studies. In this case, the brand clarithromycin, a strong CYP3A4inhibitor interaction and strong use of interaction, which employs rifampicin. We use those studies then to test the preliminary model that we built and to update some of the parameters to consistently […].So having used clarithromycin and rifampin data, we then go on to predict the effect of other initiatives indices, and this is a very rigorously validated procedure that I think is fairly common amongst all of the industry. We have inhibitors, some of which exist in the software that we use such as […]. In this case, we thought that most of these models are simply good, but again, hydroxyitraconazole and itraconazole models were ones that we found to be not quite as acceptable as we would like, and so we developed our own in-house approaches to those inhibitors. These inhibitors are validated against a well validated substrate sensitive study. Similarly, the users are also validated against thesewell known […]. So that everything has been verified that before we can predict the effect on the […]. So there's very little uncertainty left at this point in our prediction of interactions that have not been specific. So just to show you here's, here's some plasma concentration hikers showing the good concordance between the observed data, their symbols and the predictions. In the solid lines here on the right we have the drug and tablets are all in cure after treatment with erythromycin and similarly the situation before and after treatment with […] Abemaciciband year two of the active. So, I just grasp you for a few seconds, I said that we weren't completely happy with the console model that was available at the time within […]. And this was not something specific to Lilly. In fact, across the industry, there was some concern that each console model was not having the mechanistic underpinnings that we would really like. And this is led to the formation of an IQ working where more than 20 companies then combined to share data both on the exposure that resulted from administration image for console for the for the parent drug and for the […] metabolites and for other metabolites that we did not find necessary in the final model.So, so the group was able to not just combine their clinical studies also to conduct new individual work, fraction unbound, individual potencies, intrinsic clearances, physical chemical properties, etc. That would then combined into an improved mechanistic model of […]. This model was then tested for its ability to predict drug interactions and here to see the predicted AUC ratio where

you can see […] ratio could this whole group ofsubrates would take it from the picture and predict it as well. So this prediction of drug interactions, though is not unique to this new model other models without being as mechanistic as it sound as the one that was developed here. So I think this is one of the examples where the power of the IQ consortium comes into play. Here we were able to pull data from 20 different drug companies to come up with a model that was a big improvement over that big system. So then taking that model and the others that we all identified their […] or the key console that we developed at Lilly, then we were able to predict the effect of other strong and moderate inhibitors here forAbenciclib. Thank you for being compliant active species AUC that I described earlier. And then here is the effect of the thesis. You could see that the observers is predicting values here for the erythromycin and for rifampin, […] with the observations. So, one of the interesting things here is that we have a quite complex model that includes the parents and several active metabolites. This is readily dealt with by the software such as […], and you'll see the advantage of both this, this combined active species approaches that in fact, the DDI are lower for this combination than it is for the parent drug alone and this is because as I showed you, in the earlier scheme, the fraction of the metabolites metabolized by CYP3A4is lower than it is with their […]. So this lends itself to buffer, the overload of interaction and I think provides a much more accurate description of the life and drug interactions to the, to the prescribables. So we're not just interested in predicting drug-drug interactions with PBPK models, other things that interesting to be effective organ impairments and so this, of course, is a very challenging situation. For example here in the case of hepatic impairment, many features of the system are altered by the disease. Including the, you know, inside of the binding, the functional mass, changes his blood flow, sharpening, changes his binding proteins and additional effects of inflammation. So clearly very challenging. But despite this, […] requests have produced reasonably a comprehensive models of hepatic impairment and we went ahead and predicted the effect ofthe Child-Pugh A, B and C on Abemaciclibactive species ratio, and came up with numbers that were relatively close to those which we will do. So in this case, we actually did this study because we're not confident enough in the predictions of the models, I guess, you can avoid the study. You see, the predictions that are reasonable but still, I think we're not in the situation where we would we would think we could not do the actual study and that comes from data such as such as these, this is another working group that’s within the IT organization. In this, in this case, we were able to pull many, many clinical studies in which drugs had been studied for the effect and […] and along with that, each company used […] to actually build a model of the compound and predict the effect of hepatic impairment. And you can see, often there are there are some good

components […] predicted, but there are many components to which there's a substantial prediction of the effect […] and this is particularly in case you're in the Child-Pugh C, the more severe category of this […].So at this point, we were not fully understanding why is over prediction is clear. And so this falls into the category of something that clearly we need a lot of additional study to figure out how to produce […]. Another common question that comes up in an independent pharmacology program for a given molecule is what is the effect of food. In the cases of Abemaciclib, we have a molecule that that has permeability with solubility, the fraction absorbed from the intestinal lumen is very high. There's almost no way that we could see the food effect for this molecule, but nevertheless, several food effects that were good compacted all lead to end up with this new language in the label that basically says there's no effect. So we were sort of in a situation where we feel we should be able to predict food effects certainly for nicely behaved molecules, but yet, that's not something that we seemed to be received. A working group again within the IQ consortium is currently working to try and understand which molecules are the, are the ones that we can confidently predict the effects and which ones have properties that are not meaningful to accurate predictions at this point in time. So I look back now at the paper that the IQ PBPK we put together five years ago now. We were sort of drawn into this idea that we could put PBPK modeling into large buckets, large types of modeling and we could conclude that we have certain degrees of confidence in these general categories. And I, I think now looking back perhaps this is counterproductive and I think where we need to be is much more based on the subtleties of the different activities within the group. So rather than saying, you know, we can't detect that we spend a lot of time with vision or induction is a problem or diseases are the problem, that rather we should, we should take these on a case by case basis and determine that new specific circumstances through maybe for example, with the hepatic impairment, that in fact we can predict specifically for substrates and not so well. So, other sort of conclusions, such as you can't really predict natural-based interactions are also somewhat suspect. I think you've seen the case with Abemaciclib, we predicted the effects of induction. There was very little uncertainty in those predictions. So there will be no reason to say that induction from drug interaction would now be predictable. I think currently we seem to have the mindset that transporter be given with drug interactions are also not predictable. But I think that's sort of an oversimplification. We have an example here where we took we can take drugs. We can screen for an in-vitro and determine which transporters are able to metabolize them. In this case, we were looking at a drug that was really secreted and we identified that one as the main transporter and executives at the tables, were able to determine the inhibition, potency towards that

transporterfor well-known inhibitors of that, of that transporter, put those into PBPK model to make predictions, and as you can see here, the reduction in the realclearance of a whole bunch of […] substrates by these inhibitors was very predictable. So we don't really need to say we can't predict the transport immediately with drug interactions, we just need to take the other thing on a case to case basis. So there are occasions please the key. I think this is something we say over and over today. Rather than saying that we cannot, cannot do things, we simply define what are the verification limits for our users community, we will be able to decide in which applicationsthose requirements can be met.So, in conclusion,I think you can see that the PBPK framework is a […] blessing. It's really helped us toextrapolate fromour entire encyclopedia […] to the new molecules that come along and the maybe impact that the new book discovery and development is clear and increasingly in the system coming our standard piece of information and […] really nice job of putting this together in recent years […], and so with that, I'll end by acknowledging the great group that I worked at Lilly, both the Abemaciclibteam and now the PBPK group and thanks for the contributions of the IQ working groups that we worked for the last couple of years.

Issam Zineh: So our final speaker for this session is Dr. Yaning Wang, who's the Director of the Division of Pharmacokinetics in the Office of Clinical Pharmacology. Dr. Wang oversees regulatory evaluation, research as well as policy development in the division part of pharmacometrics, which is focused on modeling form drug development across the areas, all therapeutic areas and is currently the home of the PBPK program in the Office of Clinical Pharmacology. During his 16 years at FDA, Dr. Wang has been involved in many precedential reviews and policy development as well as stakeholder engagements. He's also received numerous awards for the service that has included the award merited at the FDA Outstanding Service Award. He's also served on faculty and as an invited speaker at the University of Florida, University of Michigan, and the American course on Drug Development and Regulatory Sciences, as well as internationally. He's also held numerous leadership positions. He served as a board member of the International Society of Pharmacometrics and is also a member of the Advisory Committee for the Chinese Pharmacometrics Society. With that, I welcome Dr. Wang to the podium.

Yaning Wang: Good morning everyone. Thanks Issam for the introduction.We wonder why maintenance […]given by historical comments in PBPK. If you heard those comments, that's because, you know, several years ago the function of PBPK was incorporated in the pharmacometrics. In fact, in the last few years, I think I did the largest PBPK team across the agency. And more importantly, I think I spent the most time on PBPK related research or reviews and any other type of work we need to give to pharmacometrics, maybe the same amount of time as the […], and by going through almost 200 historical PBPK reviews,working with the fellow and the PBPK team, you can say based on represents my updated view or my current view of PBPK. So with that background, I like to say today I want to highlight the readily efforts in advancing PBPK model simulation in the following years. And also to find out some of the challenges that we're still facing. Despite all the submissions were receiving instead. As any innovative approach, we in order for us to apply any type ofapplication to review, we try to do our own research,and also work withexperts in the fields. And when we feel confident enough, we create policies in order to support the news. And of course, this is iterative process and we keep learning from reviews in order to support policies for those more complex cases. And you probably have seen this slide many times, you know, we use PBPK model to quantify the impact of various extrinsic and intrinsic factors in order to make those adjustments, kind of decisionsbased on these quantified factors. And of course, these are all related to the mechanistic understanding of different factors, whether it's extrinsic or intrinsic factors. And this his represents the number ofNDA/BLA submissions to the Office of Clinical Pharmacology over the last, almost 10 years. And I have to highlight this only represents

submission to our office. As you all know, FDA now has multiple offices dealing with PBPK solutions, including our Office of Genetic Drug and Office of Pharmaceutical Quality in dealing with these foundation changes. So within our office, OCD. As you can see, over the last three years, the number of submission probably reached a peak around 2.6 cases per year. And under for […] side, you can see it relative to the total number of approval,the percentage of submission that included PBPK and so in this year, we are reaching 50% half of the solution. In this slide shows the distribution of applications of PBPK within again within the Office of Clinical Pharmacology, one publication for 2014 and then in 2017 on the right side of the more recent distribution. So overall, the DI application still represents the majority, but you can see in a more recent years we've received submissions in other non-DDI areas, and in terms of comfort level, I guess againthis both slides you've probably seen it multiple times. We're more comfortable in those years. That's in green boxes. Ready to DDI and in one absorption case, that's the BCS Class Iand in our interest, whether it's red or the other areas, we're still learning and of course we haven't had more submissions. Therefore we are accumulating voice gives us this sort of not familiar areas and support all these submissions and FDA published three guidance, that's […] DDI, the vagal DDI and one PBPK format and content guidance. And of course, the MA also publishes one PBPK guidance, and there one […] guidance. That's a format guidance. I work on highlight that we use or intended use at multiple places toindicate that again, this is, I guess, faithful purpose type of model and depending on the purpose of the model, as Don mentioned earlier, the model validation of education processes will be different. And you will hear that more in the next session. In our recent publication,we summarized the current application of pharmacometrics and the future consideration. We highlight that in the next 5 to 10 years, mechanism models, new network or real data and the new areas to receive more submissions. Your mechanics models will include both PBPK models and those system from colleagues or system biology models. So we are expecting to see and to review all the type of models in the future. In the current MIDD pilot program, if you're familiar with this that we already in the one a half year period where we received right now close to 20 cases. And of course the colors of wide range of different types of models and also different ranges of stages doing the drug development for preclinical, preclinical all the way to phase four. And among all those applications, you know, PBPK is also one of the areas we already received a specificsubmission that's focusing on PBPK.And, as you heard as part of our MIDD or […] commitments, FDA is organizing multiple workshops and one of them is focusing on PBPK like this one. At the same time, different offices from the FDA, for example, Office of Generic Drug, Office of […] Quality, also

organized multiple workshops to educate the public and also exchange ideas please experts in the fields and also talk to the public about FT the turn of thinking on this topic. And the given all these submissions and publications, we still face tremendous challenges, you know, even in the small molecules, such as you know, the lack of understanding transporter expression or activity, or lack of understandingthe ontogeny plus other things. For those systemic parameters that are really to physiology of human body. Andon the drug side, we also have limited experience or lack of competence in the MIDD or the system's ability to predict in vivo performance of different drugs and lack of characterization, a characterizationof drug distillation. And another area I want to highlight is the limited review time or highly complex models. In fact, even in the small molecule, I would argue the that PBPK review is not a single PK review, it is a PBPK review because whenever we talk about a drug interaction, we're talking about one drug effects on the other drugs in fact. So in that that we've said and just like the large molecule, it is themixtureof both PK and PB. In some of the reviews, the compounds involved areso many and sponsor will use multiple literature, articles to substantiate for example, validation or the thinking of model and reviewers have to essentially go over many papers and therefore, you know, I consider this is not a review of one compound, but the review of multiple compounds including both the PK and all the compound and pharmacodynamic interaction among all these compound. Therefore, it is coming up almost as mission impossible sometimes to review all these within the short limited, limited review time. Therefore, you know, to address all this, you know, we are still developing methodology and validating or analyzing those system parameter or drug parameters based on the FDA database. At the same time, we try to push the work back to the songs that we are trying to […] earlier, so that sponsor do most of the analysis and in front of us and at the same time, I guess that, you know, I worked with different parties within the industry, within the FDA and experts to understand, you know, where the gaps are, and by going over, I guess, almost 200 prior PBPK submissions, would not only by validate it or I guess the bottom of it is where the problems are and also compared different platforms, including the major commercial softwares. We try to understand why some of the questions or parameters are different, supported by different commercial softwares and so that, so that we can do it our own databaseto evaluate the future models, if they are different across different softwares for different companies. So in summary, PBPK submission these days is already a routine submission at FDA. At least we at Office of Clinical Pharmacology, I know our two Offices of Generic Drug and Office of Pharmaceutical Quality also are getting many submissions in the other areas as well, and yes, we're still building more experience or competencies, DDI scenario but at the same time, given theincreased number of

submissions in the non-DDI areas and also learneven our own competency those years that way, and in addition to the reviews, we try to do research in multiple areas, such as pregnancy and other ontogeny areas to support future guidance, development and legal activity because, you know, we are seeing more and more solutions and down to the areas that we have to achieve of this piece of a science developments. And with that, I'd like to thank my colleagues, especially the fellows working with me on all the PBPK solutions and their also wonderful and I will see the largest team within from […], the PBPK team and of course with the help of my colleagues from OCP IO. Thank you very much.

Issam Zineh: So let me invite the speakers up. We have till 10:00, so please make your way to the podium. When you're asking a question we just ask that you identify yourself and your affiliation.

Audience Member 1: […] from the Office of Clinical Pharmacology CDER. I enjoy your wonderful overview and very nice orientation. So I'd like to ask the panel, even drug-drug interaction has the major application of the PBPK submission. Are we comfortable enough in doing the extrapolation? Looking at Steve's example, the Abemaciclib, you have demonstrated very nicely how important are the active metabolites considering them in your prediction, then you will be able to see whether the extent of interaction is changed. But my question is, even without the PBPK inducted study or CYP3A was a strong inhibitor, will you do extrapolate this to other strong […]? From your example, we can see the differences in the ADC changes. So to extend […] interaction were not the same among the strong inhibitors or among the monitored inhibitors. Are we still comfortable with our past practice, where we extrapolate the data from a strong inhibitor to or moderate inhibitors to other drugs that are not steadyor similarly?

Steve Hall: I think it comes down to the mechanistic understanding that we have the education. So what we understand all the bits appropriately, and I think we have so that was the console example. There were models the concluded drug interactions between it chromosomes to then that leverage that other drug interactions are problematic as it was unclear on what was driving the interactions […]. So I think once we have the pieces in place, and concrete […] and the extrapolation IQ is very light, but I think what we don't have that and have run into […] as we experience circumstances that we monitor as we really […] to impress.

Don Mager: If I just ca add to that, I think, the problem was compounded right by not having perfect probes and too many inconsistence as well. So for example, in certain transporters, we don't have, have a specific inhibitors and fixtures or compounds that will allow us to nurture that particular piece. And so I think we're still blessed with imperfect data, and so I think that with compound issues, […] I think it’s a small molecules.

Audience Member 2: Changing from genetic, it is actually quite inspiring to see the PBPK workshop open with a top focus on pharmacologic. […], my related question is wanting this, the biologics PBPK application in the applied side? […] ordered around demographic data especially I noted that PBPK summary is focused on PBPK submissions and indicates what about POAs, SPOAs conductor? None one comment and the debate what biologics PBPK experienced […] and maybe doctors do all commons from the industry per se.

Don Mager: I think many of the examples that we've seen so far is the one side as well. It's really in the early phase, right? It's really more for guiding discovery, development, and many examples of others really focusing on the science I think, where we are where we're headed, and so a lot of that isn't making its way into, let's say clinical pharmacology, for example, but the potential is there. I think there's huge potential provided for PBPK biologics to help guide that process. You go just a few years ago to an immunotherapy conference. They're asking the exact types of questions, the clinicians are asking that exact questions that we were asking back in the 70s about PK. Now, what does what do we mean by dose? What dose should we get? How do we account for inter-subject variability, and on in a lot of those details that PBPK model could addressed? So I think right now, the focus is still on the science. It's still helping guide the design of molecules in early phase development, but I think the potential is huge to have this make its way into into confirmed view. In terms of how it's being used currently for them.

Yaning Wang: We do have a few, very few and I think a lack of experience, you know, we don't accept those, […]. I would say, you know most of the large molecule PK is pretty consistent and half-life 21 days with a few exceptions, and even on the other side, a lot of times, we know we can do it. There is no expectations […] monitor later. Anyway, we are learning and go serious as well, but I guess being the current […], we typically don't accept, but I guess in the future, when we have enough confidence, we should be able to assess some rare etiologic or interest subject variability. I would suggest a few more Africans, AA Development for a large molecule, that's if PBPK can address or have some clarity on that, that would help.

Steve Hall: I'd like to think that I would echo those, I think it's an area of intense activity in the company. It really is contributing to the understanding of molecules and the discovery of the molecules terms […], but in terms of sufficiency, I don't think we're there at that point wherewe certainly we are […]experience.

Audience Member 2: […] our experience from Genentech, we only have one particular it's for antibody […], to that politics […] recently be away to gather PBPK compound and […] more focused on some molecular […] similar with accomplishments, […] application. There we can rest to see where the field will move on hopefully, after a few years to similar as the PBPK in the pastto the bench side research to the clinical application […].

Audience Member 3: This is […] from the Office of […] in response to your question. A fewyears ago, we had a situation, […] where I don't remember which […] level of the, of the space on the effect of enzyme activity […] and you mentioned that there's an antique drug […] published. So then I

have a questions […] were on your side of the […] member, where some compound […], I wanted to know that […]?

Steve Hall: It is a good question even though we have a reasonably good size group of molecules, it doesn't tend to be a lot of representation outside of the usual suspects […]. So, at this point that there's no sort of having them say the ones that are most who you represented this type of metabolismnot usual association with high theories versus low theories, which might be expected as we […] more intellectual in interaction with the drugs. So I thinkwe would have hoped that we could rationalize that these outlives at a certain property. But so far that […].

Issam Zineh: That's a nice question, […] I'd like to ask. […] So part of what our objective today is to identify opportunities for harmonization as I've mentioned. I heard several terminologies and all three talks, verification, validation, qualification, and so forth. And there's a range of opinions, at least in the individuals and groups that we spoke with on you know, the need, whether there is a need or not to harmonize even sort of basic terminology around these concepts. And so maybe we can have a quick lightning round from all three on, you know, not so much the evidentiary question which we'll get to later today. But this is to have harmonization terminology.

Steve Hall: I don't think that we […] they or what it's called, you just need to […] what to expect and that we're required to do in order to show that the model is sufficiently mechanistic and predictive for the purpose that it's intended. So I think from the industry's perspective, we've sort of been told not to call it validation because maybe that's too broad, what we're doing is very fine in a roughly narrow space and moderate […] for the sole purpose. So I think that's why we kind of defaulting back to verification, not to annoy the people in […] validate. Those are, I mean, to what it should be called in […] and after that.

Don Mager: I for one like, conversation […] I concluded you set a goal for hope and adapt to that and that would be fine. But I like having a common sense approach to this whole thing. I think verification has been great for software. I don't see what's wrong with validation and just use it as a word and then forget about all the rest and I think what you have to do then is just call it one return like validation, but think through what you're going to be willing to accept or different use. Right and you know, the level of validation 1.1 or one particular week is making much less or lower than another one where to say you're going to wait […] because of some simulation that […] confidence in the model, and validation has been made. So, I don't see why we can't just call it validation and then talk really more about the different levels of each one […].

Yaning Wang: I guess you know, we face the same issue almost like 20 years ago, when we just started to supply a population of models. Back to […] same question, do we call it validation or verification or whatever word. I guess the sense was similar to like Steve have mentioned, people consider validationas a stronger or higher word compared to other words, but over the years, I guess, like he'd said, we didn't care what word we use. We just use certain criteria tosupportwhatever they intend to use we have these data, some people consider that as validation and some people consider that as qualification because the criteria will be changed depending on the intended use, while others may consider validation, the stronger word, it's like, almost like the B criteria every time you fit the same criteria, if you fail that that model, then it cannot be used, therefore, we played around with words, sometimes qualification or verification, but I guess, you know, it really doesn't matter what we use validation. We're still flexible, we still move on the criteria depending on who intended use therefore with the PBPK or any type of model, doing system type of model, we can all call it validation, but with the right mindset to say, okay telling us is different. And you may you may have to adjust the criteria, I guess to support whether the model is useful or valid.

Steve Hall: Now I think it is a particular challenge witha model that has such a diverse range of possibilities. It is very challenging to just to protect the wave it ceases to be valuable, never to be as we kind of take on the models that we develop by the […] scope of validation, it's not clear. It take some efforts to find out where you come […]. So I think it is challenging because models can […] be valuable to others […] small application space and depends for us is important, but I think that's just the challenge that we have in this area. […]

Issam Zineh: Please identify yourself.

Audience Member 4: Hi, I'm […]. I'm from […]. So my question is […] other […]. So that is I am keep thinking about the biologics. […] biologic […] but at the same time we don't see stationary […] a new interaction with the enzyme. We do see that similar […] and once we go to the PD area, we consider the future or want to consider vision type […] PBPK application. That would be certainly be a practical. There is one similar key point that you mentioned in your presentation. One of them is generalization, generalize […] and the other one is collect more biologic biological physical property orboth of those […].Well, one thing I notice as you point out in your slide, you have very detail and I've seen as what is needed for biologics. You have every detail, similar labor of requirement, release, secular label deposit. So, in one sense and that you also described the PD […] response. Basically you have a feedback and expression you have the chance to be […]. So, in a way in order to balance out the number of parameter you need, you

have to consider in this type of model the other one called generalized type of and consider that is called for nature between compartmental model, which I meant by that detailed compartment, maybe more mostly basic descriptionor copied mechanism […], but still I feel either way I still consider, I see the challenge to balance it out to either closed space […] to describe the key pass. While the other one I need to feel type of generalize or not so I can require the perfect reason. I see some challenging to edge and this path for me, […] director, is I know over in time you mentioned you see hybrid modeling if not compartmental model, particular model and PBPK model, and I you said, nicely said […] celebrated, I highly appreciated the important […] with us in terms of […] model particularly your way of […] combining habit and the PBPK model constantly monitoring […] framework to make it the same.

Don Mager: So I thinkin terms of the general platform, I don't see it much different than what we already have for small molecule. You have something for like, like some […] class or whatever platform you're using. You have a lot of options within there and so you can use that platform then to drill down to very specific models. So my point was to really begin to develop that for biologics. And right now, we have a lot of one off models for specific types, whether it's ABC or whether there are types of specifics etc. What I'd like to see happen is that we now have something like we already have a small molecule, where you have all of those options built in, you know and you can then engage those different components as needed. So I didn't mean to say that he wouldn't still develop very specific models, but starting from a general platforms starting from place where you can draw in the pieces that you need, just like you would a personal molecule. I think it's, I think it's really needed here. You have so many nice examples where the size it is important to claim it. Sometimes charge does sometimes charge doesn't, and I think, with all of those different examples is telling us that it's multifactorial, and you really need to have all of those things built in to it to really assess whether the determinants of the disposition of some of these biological constructs. And so that was my point is really just to have all those options within a common framework, as opposed to one off models that really have no more than they've ever had the capacity to build in any of those […].

Yaning Wang: You see all the outstanding, so much time on all the historical PBPK applications, and also the new ones. The more you started these applications, the more […] and no different from any type of modeling, just like property modeling as well. Because this is days, you know, if you look at all our patients, essentially, we are fitting the ability, whenever you have clinical data you just read fit the data. And I guess the original idea of PBPK model was, you should be able to predict the data based on the individual and the support system

parameters before you see all the people for conservation, but it turned out to be difficult or maybe probably because the initial system or our understanding of the system router is still not mature yet. Therefore, we end up with giving you a hybrid, you predict something to start with, with the understanding, you have a very large uncertainty, and once you have the legal, clinical data, you go back to adjust certain key parameters. Make sure the prediction is consistent with clinical data. And sometimes, you know, people may ask, how do you decide which parameters which would adjust the game of all the different parameters that can influence the ultimate. Again, that comes down to our understanding and its clearance or […] or that and therefore, I would say, at the current stage, they are the same to me. For example, if I take a PBPK model, I can say, well do I have enough data to fix any parameter with regards in order to predict pediatrics? That's the same as a PBPK model where I see, do I have enough data to say I can fix all those enzyme abundance inorder to predict the whole body clearance. If that prior knowledge is not enough, they end up with a population that's not consistent with your prediction. What do we do we adjust or […] we adjust our assumed parameters for data and fit. The process is essentially the same. And in fact, in the least my recent comparison across these soft words. The autonomy or the renal function prediction of especially for the pediatrics, if you look at every major software's rationale to support their inclusion, which are different across all three commercial softwares, which is a very empirical model building process. They took data from literature, historically, maybe eight or nine papers, digitize those numbers and fit a very impactful equation actually is a quadratic equation and then that equation serves as the foundation of the part of the on top of the prediction of living a functional within the software, you know, lets you understand those things. You know, you may think it sounds mechanistic, but the underlying model building process is looking for any inherent modeling process as no mechanistic or physiology to justification to use a quadratic equation to describe the impact of age on the […]. So, I think at the current stage, they are the same whether you fixed certain parameters within the PBPK domain to predict in vivo or in the public domain where you fixed some parameters on […] or adult decoders. They are essentially the same. So, maybe one day we will have enough data to say okay, we learned enoughabout certain parameters.Therefore, for future applications we want to change this was problems, that may become the true mechanistic or these are the problems.

Issam Zineh: We welcome any questions. So, just […] with any additional questions. So, to […] on these questions. […] you mentioned how challenging actually review is. It's time, there's a time pressure component to it, there's sort of, oftentimes we're seeing these models for the first time diminished. There's obviously a lot more complexity to these. And I

would also add their multiple eyes as audiences look and end users looking at this through the regular programs to multiple businesses are bringing this to their interactions decision making. So what has been your, what have you seen work while here in terms of facilitating that process of review and where do you see more work needs to be done? And I'm thinking, for example, timing was our first exposure to these models in drug development because as Don and Steve mentioned, this is sort of being built out pretty early in drug development and probably context where we don't necessarily need to see the regulatory decision making at that point.

Yaning Wang: Yeah, I think in the last two or three years, we've had a quite a few cases where the complexity of the […], like multiple metabolites drug is inducer in human at the same time and plus other drugs PBPK model that we're also not final and some of the model was developed based on future data within the review cycle. The reviewer, reviewers actually initially started with one maybe already turned on not enough you have to add more people to help review the other sources of information to trust you know, for example, compound ABCD, and addition to this new books at the moment, the order to say okay that qualification from the other five books as traders actually validate or supported more. This book and it just became impossible and sometimes you have to say okay, maybe, again, depending on the risk we're assessing even without understanding every detail will receive maybe, okay, the risk is low. Another area is I would think is, you know thefamiliarity of the reviewer in a certain year. For example, if the reviewer was already doing some research on the site, always some fellow on, for example pregnancy model or cognitive model, and that if once a patient is just happens to validate emails for the first time, and the reviewer applause the other fellows be few more confident because the know everything inside out, and therefore, you know, maybe other reviewers may not be familiar but as well as having one expert reviewing that domain, the whole review team should feel more confident in those applications. But again, that's a balance between your primary view and the additional research that the reviewers can't find time to do. Again, we are trying to get help from our reviewers as well as last half of the half enough tears. But that didn't work well, because a long time they turned out to be alerted tears for the reviewers versus the extra reviewer contributing to the community. Therefore, the PBPK reviewer has spent more time helping the other reviewers understand the process at the same time has to solve the real issue. So we have to work out a better way to address this at the very beginning to scopeout whether the interest reviewers will have enough expertise to handle these versus in the middle of the review, we realized, oh actually, we need another person. How did this review end and also at the same time address to reviewee. It's a challenging

issue, but we are trying to get more help from you and others to normal and more people but I'm more calming files. You know.

Issam Zineh: If there are some question […].

Audience Member 5: (Tycho Heimbach) […] I have the question first of all procedural and technical question. So I heard there's some type of review boards that could be used in becamebetween different departments of the different divisions in the FDA? So is there sort of a line between Offices of Generic, Office of Clinical Pharmacology terms of the […] PBPK models that are coming in here as part of the MBAs of the […].

Issam Zineh: And now […]. So within the Office of Clinical Pharmacology and there is PBPK oversight board. And the purpose of that function is to ensure consistency in the acceptance, the application of the regulatory policy in product evaluation. So, so that you wouldn't go to one therapy to carry and get a different answer around the application of PBPK that would carry another […]. It's also a strategic planning group, if you will, sort of where review issues that reach critical mass to become potential policy that becomes a sort of incubator aroundthat potential. There's not a cross office necessarily focused on PBPK, but a couple of things of relevance is first is, you know, in the process of developing this evidentiary framework that will be presented later today, analysis of public domain that broad multiple parties together from not just within CDER in these various offices, but others centers as well. I think that started a dialogue for kind of potentially be some governance or overview, knowledge management and information sharing function and you're talking about the others. There's an agency wide modeling and simulation working group that doesn't necessarily focus on PBPK solely but tries to bring sort of broader issues and broader topical issues for discussion for consistency as well. I mean maybe you can speak more towards that latter.

Yaning Wang: I guess, like I said, different offices focus on different things like in our office, we focus more on the DDI side but from the Office of Generic Drugs under the considerable quality.Most of the PBPK submissions are information related. They don't have to worry about once the drug enters the system, it's mainly the absorption domain. Therefore if the summarize the distribution charts, I will banks most of the absorption of zero in the DDI site. In terms of a compound interaction within MIDD submission so far, I guess we only have one PBPK focused MIDD. That's really the obstacle from a college […] of site. It's mainly handled […].

Audience Member 5: (Tycho Heimbach) […] question is how do you see the latest biomarkers, for example in context DDI? If there was some work done […]. On one hand, I hear an FDA saying, we want the data

science. We want the sponsors to submit complex new biologics in models. On the other hand, I hear that we don't have enough experience yet, so we can't really acknowledge in or improving, so your perspective please.

Yaning Wang: Yeah, like in addition to this, like any other sort of special VIP and a special PBPK conditions, you see all the applications we encouraged submissions, but before we accumulate enough chairs at the […], its mainly on learning mode because unless you learn it you will never be able to gain the experience so that's that's why we encourage you submit, so that we start the Q&A exam to reach a stage where we say okay, now we're ready to accept your whatever predictions based on those normal or biomarker based issues.

Steve Hall: […] simultaneously with the FDA is general scientist, […] trying to look and iron the pros and cons of a particular approach. So in the west or face I mean there was it was an IQ group and it seemed that the only people were limited in that sense or be useful as a […]. So, in Canada, these two things,[…] FDA trying to figure out where it fits into their experience domain and then the scientific community, as with many aspects ofthe PBPK model, the science is not finished, many gaps that we need to progress towards that leads to uncertainty. […]

Issam Zineh: […] So, let's try to ask both questions and see which ones we like better.

Audience Member 6: Oh, I was just going to make a comment. I think Yaning's last slide talking about collaboration. And I know Steve addressed some of the some of the questions, the more questions about transporters. So there's another great international transfer consortium, which were published many papers from the ITC consortium in the November issue of CPT, where it discussed indulgence biomarkers […] for a very important transport. So I think we would ask many questions as addressing the paper, the dynamic range of the changes and normal indications and how do we think it's, it's qualified to be used, but obviously, I think we could gain more experience as we see more data in clinical […] if you just collect just like […], and then the indulgence marker […] that we will be building experience that we I think, like Steve said, it's not we're here, we're not there. It's a case by case, depending on the scientific basis, it's a comment.

Issam Zineh: So one more question, I may have to be rhetorical. So go ahead and ask it and just to people know there is a break now from 10:00 to 1030. Feel free as we migrate. If you need to, but we'd like to hear your questions. Please introduce yourself.

Audience Member 7: […] Regarding their logs by Dr. Wang in terms of looking into the database, as well as trying to validate the system […]

minimalist and industry, one really commercially available software and we don't have direct access to the mathematical solutionsand coding and so on. What does that be doing to work with these software developers to validate, to verify? And what is the expectation from the sponsor, let's says the software developer?

Issam Zineh: Before we return, do want to answer the question? It's a very good questions, it also means the subject I think of much discussion the upcoming session.

Yaning Wang: I wanna answer that question. So in fact when I said when you compare with all of the commercial software's, most of the equations aren't in the public domain, it's just hard for for you to put them together. Only a few are considered confidential, but again, you can almost you know, which was likely re-engineer the equations based on pot. We are trying to facilitate the, I guess, the cross software comparison by asking the major commercial software to put them together. Again, any equations that are public or be considered can be published together, as well as side by side comparison that can be helped whoever wants to use the software, the primary standards, because like I said, the all of the data are in the public domain and all the equations that are in the public domain, it's just there's so many of them. It's hard to put them together. So we are trying to facilitate by just putting them into one table so that everyone will plan to use this software can compare themselves as well and also use your own data to judge which one is the best.

Issam Zineh: I will close the session. Please join me in thanking the speakers […].

Lauren Milligan: We're going to get started with session 2. Panel discussion on the FDA regulatory framework for evidential criteria for PBPK. It's my pleasure to introduce as moderator for session 2, Dr. Ping Zhao, Senior Program Officer of Integrated Development of Quantitative Sciences for the Bill and Melinda Gates Foundation. Dr. Zhao has over 17 years of experience in Clinical Pharmacology and PBPK, including nine years as a scientific lead of the FDA. For the past two years, he's been working for the Bill and Melinda Gates Foundation, managing the model and formed drug development for […].

Ping Zhao: Thank you, colleague for the nice interaction. Good morning, so from this point, we start the session 2 of this workshop. The workshop, this session is actually a panel discussion on FDA's regulatory framework for evidentiary criteria for PBPK, and you see, we have a panel of regulatory colleagues. Their names are on the slides and everyone should house will have the file of each panelist. So during the session, I will not spend time to introduce them just for the housekeeping toppers. So, I actually, colleague introduced me so there's no need for me to do any disclosure. That I still want to say that the views expressed in this session and at the workshop from me or myself, they do not reflect the view of the Bill and Melinda Gates Foundation. I would also like to take this opportunity to set the meeting organizers for trusting me to moderate this very important session. The session includes four parts. The first part will hear a presentation from the FDA on the white paper. And the second part, which runs about 20 minutes is for all the panelists to respond to the questions posted by the FDA. And then we move to the third part, which is a moderated session. We're going to focus on specific questions around qualification, which I believe is an area that most of the audience will be interested. And the last session hopefully we'll have time for some open discussion getting questions and comments from the audience. Immediately, let's start the session. […] presentation by Dr. Colleen Kuemmel to introduce FDA's recent article consideration of the, of a credibility assessment framework in model informed drug development, potential application to PBPK modeling and simulation. And this article has been published in the Journal of Clinical Pharmacology and Therapeutics, Pharmacometrics and Assistance Pharmacology. So Colleen, please.

Colleen Kuemmel: Thank you for, Ping, and good morning. So I'd like to start by posing a question, how do we know when PBPK model is credible for regulatory applications? In trying to answer this question, we can turn the current guidance for example, FDA and EMA. The EMAs guidance provides detailed requirements for qualification of the software as well as evaluation of the models predictive performance. These guidelines also incorporate a high level framework for modeling and simulation approaches, which states, the impact of the model determines the level of regulatory scrutiny and the need for supporting documentation and

advice. If you look at FDA guidance, it mainly focuses on time […] and recording, and as such, it leaves room for providing additional clarity and establishing model credibility. Thinking about the next generation of PBPK guidance, we recognize that the mechanistic knowledge underlying PBPK models is still evolving, but we have a better grasp of the high level principles that shape PBPK model credibility, and these concepts may also be generalizable to other MIDD approaches. We also recognize that terms describing model credibility have been applied inconsistently in the community, and this lack of consistency could lead to misalignment and expectations between regulators and sponsors, and possibly inconsistencies within or across regulatory bodies. These insights lead us to an inflection point to consider an overarching framework instead of specific recommendations for establishing PBPK model credibility. And if we could demonstrate that an overarching framework could be applied to PBPK, we could consider, we could consider guidance around the framework to standardize language and overall approach to evaluation of model credibility. And we could explore whether it may be useful for other applications of PBPK and even other modeling and simulation approaches across the FDA, and if there's value in that, that it will provide us towards the path for potential harmonization. But instead of reinventing the wheel, we considered a framework that is currently being used in medical device development. This framework was drafted by our colleagues CDRH as part of the American Society of Mechanical Engineers or ASME. As such, you'll find it referred to as the ASME framework throughout. So why did we consider this framework? Concepts in this framework built on the EMAs general modeling and simulation framework. Also, this framework accounts for many best practices in computational model evaluation and this framework does not provide specific criteria or tell users how to establish or assess credibility for an intended purpose. And it's this flexibility that enables us to apply it to PBPK. So, before I introduce concepts from the framework, I want to get alignment with you first on the terms I will be using for the remainder of this talk as defined by the ASME framework. First, the word model credibility refers to the process in a predictive capability of a model, and this can be gained by collecting verification and validation or V&V evidence. Verification according to the framework refers to assessing the accuracy and reliability of the mathematical code and calculations. That verification demonstrates the equations are being solved correctly. Validation assesses the accuracy of the model to predict observed data and the correctness of model assumptions. So simply stated validation demonstrates the correct equations are being solved. So now I'd like to briefly summarize the framework and then go into more detail about how the main concepts of the framework maybe apply to PBPK. So the framework consists of five key concepts, defining the question of

interest, stating the context of use, assessing model risk, establishing credibility, and this concept includes setting credibility goals, and drafting and executing of V&V plan. And the last concept is assessing credibility. Now within these concepts, the framework outlines tailorable stops enabling the framework to make a specific. These steps include general recommendations already described in the FDA's PBPK guidance as well as intuitive steps. Importantly, this process of establishing and assessing credibility requires a team of experts. So decisions don't rely solely on a modeler, a single modeler or reviewer. So the first step in the framework stating is the question of interest. That is the key question or decision in the development program. Next, is to define the context of us and that's how the model will be used to address the question of interest. And to distinguish between these two concepts, the question of interest maybe broader than the context of use and as such other evidence such as clinical data may be used to help address the question of interest. Now, to relate these concepts to current recommending, to relate these concepts to current recommendations, the context of use is used analogous asleep to the term intended use and the FDA's PBPK guidance. So, once the question of interest in context of use are defined, model risk can be assessed to evaluate model risk. Once you consider both the model and influence. That's the weight of the model in the totality of the evidence and the decision consequence, which is the consequence of a wrong decision, and this could be patient harm or therapeutic failure. So model influence and decision risk can then be independently mapped to a risk matrix whereby an increase in either factor leads to an increase in overall model risk. In the framework model credibility should be proportional to model risk, and since credibility is gained through V&V, overall risk drives the rigor of V&V activities and goals selected. So for example, a higher risk model would necessitate more rigorous V&V. This concept has parallels to the EMAS overarching modeling and simulation framework described earlier. So once the model is that model risk has been assessed, V&V activities can be selected. V&V activities are broken down into different aspects of the software or model that should be evaluated and these are referred to as credibility factors. Under verification, there are two credibility factors, code and calculation. In PBPK, this relates to checking the software for errors and ensuring the reliability and reproducibility of equations. As the selection of V&V activity should be guided by the risk, the rigor of verification should be commensurate with model risk. While the concept of evaluating the software is not currently described in FDA's PBPK guidance, these types of quality checks are routine in the software development. The next step in the framework is validation. And there are three credibility factors under validation. The first factor, model refers to assessment assumptions and uncertainties and model structure in input parameters. This includes evaluation of

mechanistic equations and the sensitivity of output to changes and input parameters. These assessments are already current best practices recognizing an industry and reflected in FDA guidance. The next factor is comparative. This term refers to the observed data that is compared to the model predictions. So for PBPK models compared to might be different political scenarios or populations. The number and range of competitors may be chosen to balance the overall risk of the model based on the context of use and the availability of data. So this practice of comparing predicted and observed data is also standard in FDA guidance, and industry best practices. The last factor in validation is assessment. Staffs under assessment evaluate the similarity of the model in comparators input and output. Assassins of output include evaluating and the rigor and agreement of observed and predicted data. So this is easily translatable to PBPK. So for example, for a low risk PBPK model, a user may plan a qualitative assessment of output were plasma concentration time profiles will be visually inspected for agreement. For a high risk model, a user may plan a quantitative assessment to ensure PK parameters fall within an acceptable range of air. Included in the framework is part of establishing credibility is applicability. This concept is not currently described in the PBPK community, but perhaps it's intuitive. It recognizes that model credibility increases when there's overlap between validation and the context of use. Of course for PBPK, conditions of the comparator study what exactly matches simulation. Otherwise, there's no need for a model, but computers may reflect aspects of the model that should be validated. For example, when a PBPK model is used to predict a potential drug-drug interaction, a user may validate a metabolic pathway as part of their model validation plan. So, after V&V plan is established, it can be executed and the data can be assessed to determine if credibility goals permit. If yes, then the data can be used as credibility evidence. If not, then the model can be changed or refined, model influence can be decreased, or the context of use can be revised or rejected. For some of these actions, more data may be needed and V&V steps repeated. From a regulatory perspective, we think adoption of the framework would be impactful. First, use of this framework would standardize the language and approach to evaluating model credibility in PBPK. […] improved consistency and transparency and review. Use of the framework would also create a context for discussions between regulators and sponsors, which would be particularly valuable in early development. From our initial experience, helped reviewers to frame potential issues and help industry articulate and potentially align and modeling strategies. And by increasing transparency and alignment, the framework of then the risk and therefore advanced the use PBPK and regulatory applications. Should this framework or an alternative overarching framework be applied successfully on PBPK to other MIDD approaches and from drugs to

devices. Then this offers a potential pathway towards harmonization. In the short term, we hope to stimulate discussions in the PBPK community around the utility of this approach, and plan to gain more experience applying the framework and internally. Long term, we hope to have broader discussions across the FDA and eventually across regulatory agencies on a harmonized approach to model credibility assessment. I'd like to acknowledge members of OCP, CDRH and CDER for having an excellent discussions about using this framework over the last year and importantly you'd like to thank the workshop organizers for holding this meeting and letting me speak. Thank you.

Ping Zhao: Thank you, Colleen, for the very clear presentation that at this time, I'd like to invite our panelists to come to the stage, please. So while we're preparing for the next session, which is for the panelists to respond to the panel questions posted on the screen. I'd like to ask Colleen a question. Now the white paper, entire white paper really strives for communication. And also as you can see from the last slide, it costs accommodation, and this can be in the context of multiple dimensions. It could be harmonization between drug development, regulation and device development and regulation within the MIDD different approaches or across continents, along key regulators who are leading the effort to push forward. I know Colleen that rather, the presentation that you laid out very nicely in terms of comparing and contrasting the ASMEs and more with what's currently, some of the current practice within PBPK about research, practicing industry and regulatory review practice. PBPK answer a question from me, which again, you know, this is kind of a pre-decided question, but I think it's needed to kind of give the audience especially those who haven't read the white paper or you know, have read it once and get a very strong reaction to it. Sort of both bottom line of, you know, […] why PBPK was chosen.

Colleen Kuemmel: So, why we chose PBPK? Well, I'll say that OCPs had more experience with PBPK than a lot of the other MIDD approaches such as QSP and from Yaning's talk, you've seen that there's over 100 regulatory submissions containing PBPK analyses. And so we had a really good foundation for craft pressure testing in this framework. I also think there was a clear need to provide clarity on FDA expectations of PBPK model credibility. Also, we recognized many of the high level principles and model evaluation in the framework where already best practices and reflected in our guidance is for PBPK, and I think the last point of why we chose PBPK was if we could demonstrate that it can be applied to these types of analyses and drug development, then we may be able to apply it to other MIDD approaches and this would enable potentially more consistency, clarity and review practices.

Ping Zhao: Right. Thank you, Colleen. So, from this point, let's move to the second segment or part of this panel discussion. Again, we have three

questions for the panelists to address. The first one, I'll read aloud, and you can see it on the screen as well. What parts of the framework can be readily applied to drug development and regulatory review for PBPK? What parts of the framework may need to be discussed further or modified? What steps should be considered if the goal is common invasion? So, I'd like to ask the panelists to when you first speak, please just identify yourself name quickly, a title and organization. And second, when you're addressing questions, you're free to select among all the three, you know yet for the previous panelists already, you know, make the point that you're trying to make and try to frame your questions or comments within three minutes. So we'll go through the sequence of starting with Ms. Sue Cole from MHRA, followed by Dr. Million Tegenge from CBER and then Dr. Tina Morrison from CVRH and Dr. Yuching Yang from Office of Clinical Pharmacology, and then Dr. Liang Zhao from office of genetics. So, Sue.

Sue Cole: So, I try […] to all three but quite briefly. I think in terms of the possible framework, I think, you know, […] described very well […] PBPK, but personally, I'm quite happy to see the similarities between that and MHRA guidance, with the things we felt were improved there. So in terms of considering the context of use, and the influence of the model, you know, what we call our impact framework, in terms of verification of the software, and in terms of their validation, and the comparative studies, […] happens with certain qualification or what we call qualification in terms of […]. And it just happens at totally independently. There is a group of Italian and UK Academics that are working on a similar paper based on this framework from medical devices but extending it oversight over types of models. And then not getting through the discussion around UK and drug-drug parallel guidance […] that will be published in the journal of methods and biomedical simulation. In terms of what needs to be discussed of modified, I think the scope is quite broad. So, you know, so I think the similarities, it's quite high level and in terms of what we want to see in terms of decision criteria, we might need more on that, and I see a place maybe for the guidelines alongside this framework, or more examples, you know, we've got we've got quite limited examples there at the moment. And then lastly, in terms of harmonization, I guess, so to speak, you know, we're talking about global harmonization rather than just organization across the FDA. And I mean, this is obviously a difficult one. We've already talked about the terminology although I just found out some people don't remember terminology but you know, there is the terminology qualification versus validation. We decided on qualification. I know a lot of people call it validation. I have to say in terms of the impact […], I mean, that has been used across the […] agencies longer than I've been in the MHRA and I think that is quite well established. So I think we would want to try and incorporate that somehow, but I think that would be difficult for both. With saying that, I

think really terms of what I see in the assessment of models across the agencies, it seems quite consistent, you know, we've got […] anyway.

Ping Zhao: So before we move on to, to Tina, one question for you is whether this has been ran, within the EU community, you know, people would come to this workshop, because you're the only one representing Europe at the moment.

Sue Cole: Yeah, […] of the UK. I mean one time, you know we might be not still part Europe, but […], and I have had some of these questions. I think […] discussions with some of my colleagues, but we will have to talk […] about this as well, but that I think that was quite positive.

Ping Zhao: I guess next thing, do you remember the next or […]

Tina Morrison: […] Million.

Ping Zhao: Okay, Million, you can go then.

Million Tegenge So, I'm Million Tegenge from CBER. […], that's my disclaimer. So, in general, I think when I'm looking at this framework, the V&V activity […] as we have also in the morning from the […] Industry. What this framework actually does is it tries to break down the activity that we are all doing, […]. It wants to […]of the verification as it is defined right bow with the framework. We are more focused on the validation aspect. What these framework ask is that you try to capture the verification aspect. For example, Yaning was saying in the morning, we are looking at the core, the mathematical model for prescribing aspect of the democratic aspect of the modeling, when we are using the PBPK model, we are not really looking what is inside the package of the algorithm, but these frameworks try to help us zoom now around the verification aspect, so that we look at the code, the mathematics, and then when we look at the validation, we're already doing that, looking at a prediction here, for example, for Cmax AUC, but in this framework, we are trying to do that in holistic manner, and also more in lucrative way. So that was one part we're trying to do that with the PBPK activity, we can say that whether the model is trustable or terrible or not, and also with the PBPK activity is self-efficient or not. If it's not sufficient, we are to go and look for more data, and so on. So I think in my view, this aspect again, the PBPK activity in the framework can easily be applied since we are […] makes it more transparent. It allowed, it makes more transparent from […] from both the sponsor and […] aspect. Regarding question number two, I think I still feel like we need more example with brief case studies. For example, […] PBPK modeling for example. If PBPK model using a traditional foundation approach, re-done, re-run it with this framework. Are we achieving the same objective? That kind of things would done in the future because the framework is already there, we have already […]

published […] DDI […] and so on. So, these will bring us to the next question more on harmonization. Once we have a more example, more real case studies that will lead us to where we need to harmonize or make from this […].

Ping Zhao: […] Tina.

Tina Morrison: Hi, good morning Tina Morrison. I'm from the Center for Devices and Radiological Health. This morning I […]. I, I help support senior age in terms of advancing our computational modeling programs and credibility assessment methodologies. I'm the chair of the […] committee that published the ESME […] standard. So I can be available to answer any specific questions about that. And I also chair the FDA modeling and simulation where we bring this has become a really important topic, this idea about even harmonizing at the agency when we talk about modeling and simulation and credibility requirements. Having been someone who, for the last nine years, has been in the trenches developing this framework for medical devices. Not all models for medical devices are created equal either. While the framework itself focused on what we've termed physics based modeling, you might think of as traditional engineering modeling, where you can model the actual device. There are aspects of medical device where we look at anatomical modeling or modeling in medical imaging. We also use mechanistic models as well. So with that in mind, we try to make the framework and some of its terminology general, but we were not able to be perfect at that, of course, where I think parts of the framework can already be applied, isn't the first part of the framework from the standpoint of sitting around the table clearly identifying the question that you are trying to address with a computational model, I mean very specific about how that model is going to going inform that question, and then taking the time to have a dialogue […] about and what evidence do you have that supports that question? What evidence do you have that supports the models validity? Or how much we can trust the model? And the conversation around risk? That the bar for validation should not be equal for all models, right? Some models are going to be more influential and to answer harder questions for us. From a medical device standpoint, we develop models, we typically do that because there's some things we can't measure clinically. So we may not have validation evidence for it. The model maybe the only source of evidence, but that still doesn't mean we say, Oh, well, if we don't have, you know, clinical data, then the models aren’t going to be any good. Well, we can find this specific scope for the model. And I think from that standpoint, looking at the question of the models […] or the models role and the risk around using a model to answer our question is a great conversation starter. And I think for me, that's, you can you can jump tomorrow and have a conversation and fortunately I've been a part of some of those conversations working

with my senior colleagues. I do think that from the pharmacology standpoint, you know, that's very clear that that needs to be worked on. But it's clear at the end of the day that we're all trying to understand how can we trust them all? Or where are the places where we can't trust the law? So I think from the standpoint of applying this framework to different types of models, it's already raising the important questions that we need. But then we need to have people as Million talked about is working through examples. In medical devices, I know I'm going to probably take another minute or two. We've worked through a number of examples. In the standard if you went online and purchase the standard today, there are some examples of their six in the back of the standard. Those standards, those examples stop at a critical point. Those examples were meant to introduce this new terminology and the idea around model risk and how do I translate that to credibility goals, with the examples of the standard do not do is to teach you how to do the credibility assessment piece. Once you have all the information in front of you, how do you make a decision? So that's the places where I think the examples are going to come in handy. In fact, what I even suppose is that you give the same modeling data sets to different groups, and they work independently to identify the context of use the model risk, the credibility goals, and then make an assessment at the end. How and how do they think a model to turn that question and then compare what did are these five groups come up with. That will allow you to look at some of those subjective nature of the framework and some of it that may not, you know, at the onset appear to be quantitative. But there are we've done some of this experiments, if you will, in medical devices. So I think that's a really good place for you guys. Not just having people rework the examples but having them do that in separate groups and then coming at the end together and having a conversation about what worked and what didn't work. Thank you.

Ping Zhao: Yuching?

Yuching Yang: Okay, so I may only be […] basically a lot of this concept and the not […] and to be honest, a lot of the concept has been applied routinely as […] that’s the part that we do. So as emphasizing Yaning’s talk and you can see what these slides, […] use. So, basically that is already covered at least a couple of points on this framework concept. And as emphasized in this framework, lucky it was accessible submission. PBPK submission is to demonstrate the adaptability of the model for […] post content of us. So, for me, this framework have two benefits. First, it provide more clarity from a regulatory perspective. What is a fit for purpose? What is the context of use? We laid out very detail about what is our thinking from review point of view. What is, how do we think, and also if provides these framework so it can arrive long discussion and expectation among not only within the Office of the

Clinical Pharmacology, but also with the agency, as Tina pointed out, and also they will be responsive. That is one of the, they talking about to help us what it wants. And also, finally in this framework, we can have more structure, and the more effective is crushing each of the components. And then in terms of the application and use the upgrading potential for use of this framework, you know […]. So by evaluating a model difference, which is a component between the model impact and the clinical data, and also evaluating the decision consequence, which is we which including both regulatory and the sponsor, we can identify an optimal training home […] and establish credibility goal for the model. So have these over, overarching framework to establish evidentiary criteria is very critical as some point of the earlier comments, but is not an easy task, as Sue pointed out, so I do hope that we can move forward to a harmonization by opening up this discussion. This is just a starting point for everybody can look at the same picture, sinking in the same direction, that is probably […] align as an effective discussion. So, in a way, with substantial number of the submission and […] from different stakeholder, a PBPK stakeholder, including academic, industry and regulatory. I think we really have a really great foundation to explore this type of framework. As a reviewer, I'd really really like to see how this framework can help the review team to communicate from their area of expertise and the reach consensus on the regulatory decision. So, of course, when surface first, we need to actually practice. We need to actually practice these framework. So we need to, we need to cover this about across different part of it. We need to be confident and comfortable about how to get final context of use, and we need to learn how to evaluate precision consequence. So […] while these framework is hopefully to have a transparent process on the nation of another risk and the selection of […].

Ping Zhao: Liang?

Liang Zhao: My name is Liang Zhao, […] modeling, Office Research Standard, Office here in the Bronx. So I'm here before, actually could be the last speaker for this. This is I agree with […]. So, so actually before I just want to make some comment about things in practice. Before I joined FDA. I worked in the industry and worked as a consultant for modeling simulation. So basically, if you read through the three questions. Question one, whether what parts of framework coming ready for practice web development and regulatory review called PBPK. I think it kind of a mental game, the monitors plane every time you are facing a problem or product, then I think the subconsciously of all the this framework regardless of what terminology they're using. So, question to work practical the framework can be need to be discussed further or modified. I think I still have some questions regarding you know, the distinction between defined conference used, assess model risk of

question of interest. You know sometimes it's, you may find this hard to half of the things separated in a clear manner also regarding with establishing credibility goals. So, you have plan should you have a separate section to lay out the credibility goals and then you also need to establish that way of plan. So, those factors in the report, you already have step two analysis […] plan in place, should we also have verification and validation plan separately or invalid in other reports. So many in the practice how do we differentiate those sections to make more like a martial arts, so fluidity. So, fatherlessness may signify a really good master. So, to be a model with this framework creates some really rigidity, so should […], you know, seek more input from others investigation in terms of implementation especially from throughout the industry. I believe that the part of the plan. So what steps should be construct the goals of harmonization. I think the harmonization is a very big point. If we do not have a will have seen cases in practice. Smaller learning process is everything is evolving. If we can see more public report and I have a very nicely laid out sections was the contacts to us what how that'd be fine. Or that differentiated from assessed model risk. How the model risk differentiate credibility from validity of plan. You know how to ask you to then have a plan. I think those things, hopefully not create integrated into the, into the practice, I think is more cases that can be shared in the public and the shared among the modeling field is the key. And with that we may have come to a consensus that's usually magical on a practical sense.

Ping Zhao; I see that Tina is ready to respond to some of your questions.

Tina Morrison: Well, I think you made a good point about fluidity. In fact, it's important to understand the perspective of which a standard was developed. And when we put this process map together, the idea is that if you are starting out, you might follow these steps. And of course, that's not always useful for an industry where people are already, they already have emission evidence, they want to know what they can do. So we have, we've taken on some exercises and say, I have this model. And I have this validation evidence, what context of use, allow me to, what context of use that I use the model for if I have this much evidence with this model. So you know, while it is a, you know, it looks like it's a rigid process, I give you, it's just an opportunity to take a step back and say, how else might I be able to use these concepts to communicate different ideas? So I think there is fluidity it's not, it's not explicitly written that that's a way to do it. But we have some of our folks interpret it that way. It's like I have this model. I just want to know what I can do with it. Not I want to set out and solve, have this model and do this particular things. I think there are different ways students Look at it.

Liang Zhao: So, while I'm sitting back because […], you're really, you have those modeling product. You know my […] of data. We have data extraction methodology […]. Then you have the validation approaches. So, I'm referring to community met really means in reference to the format and the format should be separated actually in this way or should we just depending on how bigger the problem could have been, just to follow the report, […] the report, you know you have the place all the elements in different parts of the report and at the end, the reviewer […] the reviewer's perspective You have all the links and you find sufficient, sufficient verified, validated for the purpose of use.

Tina Morrison: And you describe a really important challenge is a static report. And I think when we come to the next phase of the questions, I will have a chance to respond to that with respect to changes to a model and changes the software. The one of the challenging is like you give a static report, that's a timestamp in a particular phase when all these things are really important. So, interesting to think like beyond where we're headed in terms of regulatory evaluation and pathways to providing some common effect.

Ping Zhao: […] before we move to the last section, which you know, the […] very good question and I think it's very relevant to the sort of, you know, like a specific discussion that you mentioned that you know, you for the four steps. It'll be nice to see more cases. So I'm wondering, you know, whether if the team has received similar cases where people already applied this methodology. I mean, you chain or you know, maybe you can speak to that. If it's not, it is highly […] company, Why?

Yuching Yang: Yes, we do. I mean, this framework by either was possible, of course we receive from the PBPK oversight improved. Everybody trying to put, […] through this framework. Basically as described is basically, we already are in the process. We try to separate the component and then try to put it in. And while we do that, because we want to see you guys thinking this way. Can we think on the same page? Can we talk the same language? So, it's not the value of, probably, […] in the past. It basically have a new offer, new workflow. And yes, we do have […], you know I am these stage, which has proposed to follow this framework to display a modeling approach, who displayed their verification play and also internally we are getting some kind of new submission of the end stage of IND stage or NDA stage, we will have internal practice to see how can this framework help us to align our decision is catchy and why are we come to a different result, which means maybe certain group of people will have a different conclusion in terms of the impact in terms of how the model risk is high or low. Either have a different verification threats, but that it is ok, but right now we know what we are discussing. The difference is either

interpretation of the model risk or interpretation about how you have come up. […].

Ping Zhao: So I think, you know, the responses to this request appear overwhelmingly consistent and gives a lot of hope, actually, you know, it's possible to adopt this overarching what it called the generic or general framework in PBPK. To further, some of the, I call it demystify the you know, the dilemma here is I need to point out actually an article, you can read it. It states very clearly that the standard does not prescribe specific activities or defined criteria required to establish model credibility for a particular context or application. I think Tina mentioned that her response as well. And, you know, this is the past several months also have been very instrumental to myself in terms of digesting this white paper and also, in parallel kind of get to be more familiar with the device colleagues have been experiencing in the past maybe 30 years in doing this kind of thing. And what's encouraging is to see how the things are really converging, especially like this to mention that there is also a parallel application coming from the Belgian and Italian colleagues on applying the framework and the disability of PBPK field to adopt the framework. So I think we can really, you know, see a lot of upward momentum moving forward with the, with the adoption of the general framework. This is why I feel like discussing with the panelists individually, and also we had a meeting. We felt that we're better this is the rest of the panel discussion to sort of go back to the problems that we have. Right. So the key question many people would like to know, like can be to mentioned, you know, the things that held audience of what the regulators want to I think it really boils down to qualification. So it's like, how do I feel confident about PBPK at the current stage and Steve, you know, in your call, you had a very nice common about, say five years ago, when IQ was talking to FDA at that workshop, and we sort of like draw the broad stroke of the landscape, right. You know, what is high conference, what's low confidence. It is somewhat, it is somewhat counterproductive, as you mentioned, I told it a great because in a sense, you're sending a very kind of weird signal right and so if my model is low confidence, your management or you know, the FDA review to say, why bother doing this, but you know, the, the landscape actually, you know, moving forward, what we can do best with really change the status of each individual application and even maybe fine tuning within a broad […] you know, category into transporter bay's TDI, you know, diverse looking vision natural thing and community and not only the evidence accumulated but also the, the pass way that the regulators can tell the field. What would be considered as acceptable? So getting back to this accessibility or let's call it credibility assessment using the framework term? I'd like to really ask the panelists to address specific questions which is around the model qualification, which is more of the EMA term and the FDA to a […] like predictive

performance or predictability, which really refers to whether you have enough time that you have done many glass as Steve mentioned in the in this call with me the other day on the left hand side, on the right hand side, whether your model modulators, PBPK models have been qualified or you know, verified, validated using this term, whichever term were using. So I like to start with Leon so Office of Generic Drugs is now very active in PBPK research and we have begun to capitalize research to support several reviews and some of the reviews have to say are very challenging, especially in the field of local acting drug products where it's very difficult to find the right competitor, again using the framework or the competitor may not be directly relevant, again using white paper term. So how does office manage the way the challenge equivalence assessment is literally, let's bring it within the local acting class.

Liang Zhao: Thank you Ping. If challenge is a big on the unit or locally acting product or system with the acting product is fairly straightforward, all we can do is rely on the systemic a concentration of plasma or serum concentration, make a determination whether the product is equivalent or the product delivered sufficiently to have to have this act. So, follow the action product, you know the sometimes the concentration drugs response the detectable in the blood or it may not reflect the local drug delivery, really is both a challenge for generic drugs and new drug development. In that case and for different organs we do have different strategies and that also it involves some technological advancement. So, we also take certain the other race of the base approach plus the totality of evidence in that regard, in-vitro tactic play a very, you know, to have value in terms of the drug delivery rate or improvement assessment. Currently the, you know, we have to we have to rely on, for challenging cases we, have to rely on […] cases, we have to rely on individual or […] data that's indeed directly related to the drug delivery or drugs for the status of the action. So, for example, for the skin for the multiple […] drug application of our skin we can use somehow acceptable using human excised skin to conduct in-vitro permeation task. You know, the next technology, next generation technology could be natural dialysis and open for macro profusion of those technologies directly matter of the direct competition and the cutaneous space. Then with that, we can verify the PBPK model with actually observed satisfaction for already hailed products. Very big challenge we all know this year we have generic approval or running out of air. So is a drug with a cumulative model I think, hundred million dollar sales. So for those products many regional […] application of the drugs, the drug activity so we are not ready yet, […] synthetic drug, […] out with the central peripheral drug application […] administers. It’s really a challenge and that we could open opportunity for the modeling field that they can combine the computational fluid dynamics model I think that I […] model modeling approaches with PBPK

approach. Once we can predict the long regional […] PBPK to predict the drug of adoption, then link that to the systemic circulation. So, with that we can use some realistic model. Realistic model means we can […] like experimental models that can represent the local affiliate physiological environments all the geometry of the side and the dragon action and we can use in-vitro experiments. For example, […] model. We can use in-vitro acceleration of the product. We have the drop into the realistic model can predict track degradation on that realistic model. So, with those things we can indeed, verify the PBPK model or other type of model whether the model can predict you know the key staffs of the drug performance. So, the field is obviously bobbing and we have in the one period between 2017 and 2019 doctrinal grants and contracts dedicated to this area. We are already investing more so, certainly we can share with the field and it will progresses.

Ping Zhao: So we move to next to Million. So, you had a very nice responses with sweet questions from seekers and […] emerging. In your opinion, what are the major intended uses for getting this, this has been brought up for the first session.

Million Tegenge: […] session constant of this equation, but at sea bar, we are at the stage of applying […] surprising for conventional biologists […] see what is a much more complex product and merging product. For example, […] therapy product. We have vaccines, preventive vaccine, which are complex, sometimes in their population noting on this allergy, but we can have adjuvants added to moderate the increase response and some of these adjuvant are becoming noble in terms of how they are moderating the response. So with that, currently […] with regard to PK, but when you are looking at PK in this complex biologics, I think we need to redefine it. I agree with the morning session that PK and PD are mixed up, but even I think we need to come up with a better definition. For example, in boxing, we don't really the PK of […], we rather collect the response the keyboard and a way of trying to characterize the endogenesis from […] with some kind of some kind of correlation assessment and we try to predict efficacy. So with that, I think the major challenge is data and also understanding the PK, let's say for now PBPK of this complex product. For me, also […] may seem a challenge in terms of understanding the role of Charlie, and understanding the visual logic, particularly some of the product we regulate […]. New tactics plays a major role, but the number of unknown or copied in understanding the archetypes of the molecules. We tried to collaborate with ethnicity or nationality […] in understanding the new updates of vaccine activity. One of the experimental what we have done, we have done also some exploratory understanding updates of larger molecules with a bigger experiment, she is a good model around understanding the budget that much is used in I know in pharmacology. So there are some data, but we are still struggling

understanding that theology of particular the physiology of the cycle of administration that for vaccine innate immune system is activated at the site of administration and we are majoring response, the study in the blood and that the type of analysis is challenging from a quantitative aspect, but it is also an opportunity in terms of in terms of to be this type of analysis because sometimes experimental studies are not feasible. So, if you understand the relationship then we can make make a prediction. With this in mind actually, CBER conducted a PBPK analysis for noble merging vaccine adjuvant, […] containing adjuvant. These have been used in Europe two years ago, but until recently, we never seen containing […]. So as part of the analysis, we conducted an exploratory […] analysis supported by some experimental analysis and the PBPK analysis actually shows the major contributing factor in our sensitivity analysis, […] which we don't know much. But these will help us to predict the bias divisions of that too, but mostly it's a mechanistic prediction. So that's one area we are looking for opportunity around PBPK. Another area is for advanced therapy, […] therapy product. This morning we have about half T-cells in the […] T-cell approval, we use conventional departmental modeling to understand the effect of a sensational drug-drug interaction for example. The incorporations of example, the implications of positional, how it is impacting community sale parameters, parameters, parameters, select tentative parameters such as the expansion phase and the construction phase. I also noticed that illustrator there are publication coming out. T-cell based therapy kinetics. T-cell based kinetics profile actually […] since 1990s, but recently with the emergent of cognitive type of therapy. There are acting around the world of PBPK type of modeling and also some kind of risky model. I think these are some […].

Ping Zhao: Thanks, Million. So, next question is for Tina. This has been sort of touched a little bit in the second segment. You know, in PBPK world, there are platform software being updated. It is not on a daily basis […], at least on a copier basis, but different versions will come up with a particular knowledge and you touch base on how a device is not, number wise not create, you know, that the models are not created equal and number two, it's not static, right? So how you just tell the audience and they're overarching framework how the center has been managing the modern changes.

Tina Morrison: So there's a number of different ways to go with this question, which I think is a really important one. The first thing I'll say is that under the software as a medical device program, so that's where a software tool would make a kind of therapeutic or treatment or surgical planning decision. We have a pathway, depending on the risk of the device that allows for that software to be put on the market to answer those types of questions. When those devices are evaluated in the

material that comes if the, if the software is a 510K or a class II moderate device from its pathway, and its special controls and how those devices are regulated. There's information in those special controls that describe what types of iterations to the software would require additional review by regulatory agency or just firing notification, but in a brighter sense, where this field of modeling and software and the lines are beginning to blur. I think our digital health program at CDRH has been growing tremendously and all of the aspects of software as medical device are being reviewed under the digital health for those of you who might be following the digital health aspects like software platforms, even aspects that have mobile apps, for example, are all being assessed under this pathway and mobile apps and software tools get updated really quickly. And those timescales are really different than timescales in which we do our regulatory reviews, right? So, one of the things that the digital health program is working on is a new pathway. Right now this pathway is being piloted. It's called the pre certification program. There's a lot of information on fda.gov about the free certification program. There are nine companies that were invited to participate in the research program. The gist of the program is that once the company presents the platform tool, whether it's software that's installed on a computer, whether it's a web service, whether it's a mobile app, for example, there is that initial pre marker review. But then going forward, what happens to those organizations is that they undergo an appraisal assessment and excellence appraisal assessment, meaning if the organization is meeting certain metrics, in terms of organizational excellence, quality, maintaining safety, once the devices on the market and capturing real world data, this requires the use of sort of product life, product lifecycle management platforms. We are really taking in real world information incorporating back into the system real time, it's really challenging when it comes to sending a stag report to the agency, right. You have to kind of freeze everything which is really impossible to manage when you really want to get that real world information and keep updating and improving your models. So this program is being piloted right now. And under these appraisal metrics when we're thinking about in the simulation ground, because many of these software tools have some aspect of a predictive model in the software package. We're thinking to ourselves if you know if the number of simulations starts to increase sacred for CDRH, we're not going to be able to on a case by case basis review every single model that comes in, could we consider the possibility of utilizing these appraisal metrics for assessing a modeling and simulation say, enterprise that a company, many of the companies they develop these models that they want to use in a number of different products. So in the CDRH regulatory science priorities that we just published for 2020, our goal is to start working towards moving past of rigid framework where we're using that as the foundation towards developing appraisal

metrics. Let's say can we get to a place where we allow the organization if they're meeting the certain metrics to make decisions about the model and the model used, and at what point, when does FDA come back into the mix? We haven't figured that out yet, but we are working with the industry to say, you know, we understand that there's a challenge here that we can simply slow innovation if we have to review every single thing. So I would say keep an eye on what's happening in the digital health program and see what kind of learnings can translate to PBPK software platforms in the coming years.

Ping Zhao: That's very interesting. So before I […] for Sue, […]review of question, Tina, so this is very important. I do have a question around, you know, having this excellence of resource assessment. Imagining, you know, the PBPK platform, what goes with this […] someday, right? Does, what kind of incentive would this cut off program provide and that's one thing. And second thing is […] really good because it kind of set a high bar, hopefully on the comfortable follow the rigid kind of a more rigid, if you detailed kind of requirement, […] ability. But then wouldn't it be possible for, for them to just show around and say I got this pre qualifier, no I admire this OCP cases, then does that mean that they can, you know, let go part of the V&V? One, they use the digital products to do some prediction, it could be application tools in the application, […] on a specific and far more generic equivalents assessment case. Could that be kind of a part of the evaluation that has been done.

Tina Morrison: So that's interesting. So I'm going to go back to the first question about the incentives. With the nine companies that we've been working with, including Apple, Google, Johnson&Johnson, which has a benefit of legal for medical device company and the drug companies. I forget the names of some of the other organizations. So the benefit is that the regulatory process is kind of tailored to the product. So instead of having a fixed regulatory pathway, so for devices we have high risk devices undergo a pre-record review application, versus moderate risk devices which undergo this substantial substantial equivalence where you compared to a product that's on the market, the regulatory pathway will be tailored for that particular product. So the appraisal metrics would be set once the initial review was done in the benefits of the company's That, as they maintain that excellence as they maintain quality as they need to transparency of safety to the community, that they're utilizing real world information to keep their products up to date to improve the safety of the products, the effectiveness of the products. You can imagine what happens with that kind of transparency publicly. There's an incentive for the organization. We're making a big push at CRH […] patient centered medicine, patient preferences, patient outputs, you know, patients they want more say in their health care, right. So they know

that a certain organization has a certain excellence appraisal, you know, I would say personally, patients will start speaking up for that. So the benefits then become less regulatory oversight from the FDA and more engagement on what's actually happening through the software platform. A side piece that we're also experimenting is how can, this is through a pilot project, how can we invite, how can industry invite FDA into the platform without having to submit the static reports during the regulatory process. So there's a lot of interesting things happening. And I think that will also go partly to your second question of being around, you know, trying to imagine a platform that that would, you know, serve the needs of all these different centers. I think it's great that we're starting to work together now as we, as we get towards that future where those lines start to blur.

Ping Zhao: Tina, […] question, if you can […].

Liang Zhao: So, […] app appraisal of review, company review. Today, half of the […] section 4 of the […] strategy following this framework on this kind of integrated into the whole package?

Tina Morrison: So I'll just briefly say the framework just came out just a year ago, and so we are implementing it in our regulatory processes with the development of the guidance document. But there is an app has a predictive mathematical model than yes, but if the software app is you know, […].

Liang Zhao: Do they have […].

Tina Morrison: Yes?

Liang Zhao: Do they have […] before?

Tina Morrison: It depends, so we can chat offline. Okay.

Ping Zhao: That was a very nice discussion. It's definitely a very educational. Thank you, Tina, for the interaction. So the last question to the panel from me, it's actually the same question for your Tina and Sue, and Europeans reviewing PBPK on a daily basis. So if this framework is adapted, do you think this will affect your European practice with regard to the evaluation or consideration of model qualification? Maybe Yuching can go first.

Yuching Yang: Regarding tool performance of qualification, these people cannot, another stage on this specific function, no either way or not be impacted. So, in a way predictive performance of a PBPK model is based on the state of the science and it should be defined and agreed within a community among all of us. So, as I mentioned earlier, the PBPK king, […] OCP, we accumulate large knowledge base. So, we can keep up and keep updating in terms of our daily performance,

specifically special report a regular carry application. So, CHRE at this point is playing an important role, but we defined long contact of use after reject oppression of the interest. So this two is correlated. But on the other side, the credibility requirement, mind PBPK with your content of reviews, which means the model which is another product or another for one, content of use maybe good enough or sufficient of another […], you know, for example, your PDF should be another another […] credible enough to support a dosing recommendation in the absence of any critical data. But a model may be credible enough to support an dosing selection for pediatric population in our IMD stage so that the same application will go with some the new, new safe activity interaction, identify, build a new science and our passion we use this new technology on new biomarker finding. We really excited about those finding, but we really encourage this kind of discussion happening in the earlier stage, then we can see that together to notify low criteria to custom make of criteria, especially […]. Do you see in this framework list in interaction, as Liang pointed out. It will be an interactive process. So at the refining part is one important component of this concept.

Ping Zhao: Sue, anything to add?

Sue Cole: […] across Europe. So I mean, I can't say that, I think we gain places and I do appreciate that within the […] the source that they have, the FDA. So if […] framework that can be applied across […] models, relation models, or […] and objects in terms of molecules and you now, the generic setting as well as individual application. So the total framework, and I […], but in terms of assessment of PBPK framework, item 3, […].

Ping Zhao: So we do have about 10 minutes. This will be opened to the floor. Anybody can ask questions or comments to the panelists is…

Audience Member 8: Firstly, I want to really applaud FDA to taking the initiative building these. They are comprehensive framework and especially leveraging other computational modeling disciplines experience. I have two questions if I can. First question is really more about analogy to the device, which we are averaging to a fundamental question intended for this. I admit I'm not an expert on the device, but I learned actually here in a room back in the office for those a public workshop is device are also evaluating revealing in different waysdepends on the use. If it's independent assertion, the devices have driven the decision. This need to go through because reveal, but if the application of the device is more within the label framework as a supplementary permission to make decision that you don't necessarily have to […]. Then regarding modeling simulation, I have a question of what is analogy you tend to use for the typical models measure software and also for models innovation software. For […] software, they tend to use for flips or whatever, for either nominal whatever was in the TV intent of yours is by using via scientists, doing analysis to make researcher develop decisions is not for the software to independently make a decision that whoever the user will follow, and even for model simulation analysis in drug development, even if we are making extrapolations off, for example, to a model […] inhibitors were given for a different dose with different patient population. We have a lot of our supplemental habitats. The model simulation output is nearly one additional supporting piece of adjuvants with different level of impact. It is the addition of […] to allow other observed data from clinical work for clinical, like a clinical DUI study or in-vitro […]. So we never make, at least personally, I haven't seen that independently making a drug radio number decision purely based on modeling. So can the panel please comment on this difference over 10 years abdominal and how to leverage this framework in the models?

Tina Morrison: So it's a really important question that you raised, really complex, I'm going to do my best to be succinct because this is where terminology really matters. So for medical devices, yes, they haven't and use how the device intended to be used, which is very different than the intended use for the model. So let's first just think about medical device that has no software model component in the device. Modeling and simulation can be submitted to support performance aspects of that device. So those would be reviewed in the regulatory submission of the medical device. The V&V framework is really kind of set up for that scenario, right? We intentionally use the term context of use, so it's not to confuse or, you know, relate the intended use of the device with the context of use, because you can have scenarios where you have a high risk device, a high risk intended use with the context of the use of the models look, or vice versa, right. So when it comes to software as a medical device, you can have different ranges of classification of software as a medical device. Software as a medical

device will have intended implications for use or unintended use, because it's a medical device, it's just software in nature. You then also have the added complexity of potentially a predictive model being in that software which would have a context of you so that those terms were intentional to be able to make distinctions in terms of how we review the simulation versus how we repeat the device. So there can be standalone software that has an intended use. But we will try to work the framework to think about this and such and the questions that we asked about the predictive tools.Do you guys want to add anything? So there was one more thing I wanted to add, but Iwanted to make sure that others had a chance to respond.

Ping Zhao: We will be […] standpoint of […] the pattern of the data.

Colleen Kuemmel: Yes, so the way I see the context, as Tina said, it's how the model to address the question. And, and that's also to be said, the other objects, such as clinical data, may be supportive and to view it as the totalityof evidence. So modeling plus clinical data, and viewing that package together. So something that's analogist to a,to CDER and have the CDER as a tools program. When CDER has drug development tools, which I believe some of the software platforms you're talking about fall into that. So that was the third point that I wanted to make. For senior age, we have a medical device development tools program, where we have software tools that can be evaluated, or computational modeling tools can be used by multiple industries, right? In the same way that you guys have the drug development tools program, and you talk about qualifying that software. So intended use does not come into play in that scenario, because it's a tool. So the tool itself should have a context of these statements. So again, I know that was quite a difficult but important question that you raised, but there are distinct ways in which we can look at and I believe, at least from a drug device perspective. […] the same place. I hope that […].

Audience Member 8: I have some more related question, more of clarification for the definition and expectation regarding notification as in the white paper, because to me it seems like the verification needs whether the equation is coded correctly in the software platform and whether the equation is solved correctly whether the new foundation offers some […] and the PBPK when a lot of […] software. There are two challenges. One is whether it's coded correctly in the software platform, many times the sponsor doesn't have the ability to see and the other the next level of complexity is whether the equations are solved correctly and even the motivation […]. I'm talking about harmonization of broad application of these framework and Id either for global population PK modeling, which has been pretty mature in the past years, I do not believe for global phenomenon as we go into the

detail of verify whether the migration algorithm are ready or not, or watching bandwidth probably came on. So appreciate a clarification. Maybe from the panel of what expectations for the verification.

Yuching Yang: So our presentation, you cannot take away […] often talking about variation is what you're currently pointing out. […] in the sense of observation, […] wave oppression will be. Do we really need to hear about the verification of any product? We do need to know is this model fundamentally functioning normal? And I meet at FDA, at least for DPM, if you want me to evaluate the source code, ala compiler, and how different the integration of the 45 group versus the 50. I will not be able to do that. That means this is not something we should not consider. So specifically for you, we currently, we do not know how to go to this activity, […], but we do have a consensus. This is one component we need to look at and this […].

Million Tegenge: The verification and the validation exercise […] is actually in connection with the intended use. Each of intended use is for example, for predicting rain concentration […] physiological and […] parameters could be appropriately capturing that specific aspect. So we have to also understand that […] open source versus some type of industry standard, which we may have more experience in.So it's again, the verification exercise is conducted is intended to so it's not supported activity. And it's not prescribing to specific aspect. Also, […]

Audience Member 8: […].

Tina Morrison: I'm sorry, I really do want to say something with respect to this because I think it's important. I know the gentleman behind him is waiting very patiently to ask his question. If if there's anything I can answer, I'm happy to say five more minutes. Because this is really critical. In particularly in the engineering domain, where we have lots of software platforms. It's really on the onus of the user. And I see this as as chair of the V&V Committee, where we look at modeling across industries from oil and gas, nuclear aviation to medical devices. You if you're purchasing a software tool, whether it's open source, whether it's commercially viable, it is on the user to be responsible to know what's happening behind that. And if industry is saying there's tools on the market for those, that information is not available, you guys need to come together andpush thosemakers of those offers to give you more information. Because my personal opinion is that is not on FDA to review source code and determine how verified your model is from a coding standpoint, or numerical accuracy standpoint. The users and I'm really hoping as we move forward with this framing, and we can be more explicit and FDA […] more specific and its guidance document about that. So I would encourage you to look for that information. This is really a critical point.

Ping Zhao: Please 1 minute, Mark,

Audience Member 9: I'm Mark […], Medical Research Group. So I'm standing here you're answering some of my question already. So we'll be brief. But to this issue of software versus models, it's like, I think there could be room for more clarity in the white paper about what we're talking about here. And if there was even some discrepancy in the panel, DrKuemmel talked about verification being a software thing, whereas Dr. Tenenge and Dr. Wang earlier this morning were talking about verification of the model itself the model equations. Would it be, I think it would be helpful, if there would be some statement that this credibility assessment is focused on the model or on the software and then the last discussion we're just going on was talking about those sorts of activities that are required for software verification validation. If we can disentangle the two, then we can have an understanding of the science which is really captured in the model and the Computer Science, numerical algorithms or software.

Ping Zhao: If I can speak to that, Mark. That's a very good question. Took me, again, you know, a couple of readings of the white paper. I think my take is, this is about the model is like a, you know, the industry submitting a case. These are the requirements are expected requirements, way to present your case, no matter you know which platform or software you're using. So, hopefully that clarifies. With interest of time I think I have to close this session, like really sank all the panelists and presenters for the food for discussion. And hopefully, you know, we have a fast forward for question number three and. Thank you very much.

Lauren Milligan: Thanks everyone. We're going to be breaking for lunch till 1:00. Apologies for miscommunication of a time ordered lunch, they are bringing extra lunches. So please, you know, feel free to see itfor everybody. Also, feel free to eatfor lunch if you need to and return on time second […] at 1:00.

Lauren Milligan: Okay, welcome back everyone from lunch for session three of PBPK case studies. Please welcome this moderator for session three. Dr. Shiew Mei Huang, Deputy Director for theOffice of Clinical Pharmacology at CDER FDA. Dr. Huang has over 15 years of experience in drug development as well as 20 years of service to the FDA.She served as president of ASAPT and and recently won the Henry ElliotDistinguished Service Award. Dr. Huang.

Shiew Mei Huang: Thanks Lauren. Good afternoon. So welcome to the session three. We'll follow session one's format will have three presentations followed by a Q&A. So this morning, we have heard about the PBPK 360 and the state of science from industry, academia and FDA, followed by the discussion on regulatory framework on and intentionally criteria PBPK. So the session will use cases to you toillustrate the applicability and challenges in using PBPK from a regulatory, academia and industry perspective. So the first speaker is "Susie" Xinyuan Zhang. She's a PBPK […] in the Division of Pharmacogenetics. So in this role, she provides oversight on all PBPK submissions on Clinical Pharmacology, to our office. So then she has done that for two years. Before that, she was a reviewer for IND MBAs general center pharmacology issues and prior to joining our CPE, Susie was an […] from the Office of Research and Standards, where she used the PBPK to address various issues in a AMDA control correspondences, citizens petitions, […] codes guidance development. So she has a lot of experience in PBPK, not just in clinical pharmacology application, but also in generic drug development. Today her focus will be on […]. Susie?

Xinyuan Zhang: Thank you,Shiew Mei for a nice introduction. Today, I'm going to talk about the case studies based on the PBPK modeling simulation submissions in the Office of Clinical Pharmacology. While everybody case studies because our confidence in the model prediction simulation is viewed upon the case studies. So here we go. For today's presentation I'm talking about five cases. There are complex strain mediated drug-drug interactions, […] about induction, something about metabolites and now talk about this big populations as well as transporters related issues with PBPK model simulation. On the first three case studies were selected based on our recent review experience where we, where we see these issues coming up for more than twice or three times and two case studies were selected because I think the whole community is interested in knowing the current status as well as where we go. I have a disclaimer here that examples for each case study are not all inclusive. They're based on my random comes in action. So far for this, you probably want to go to drugs at FDA. Case number one complex CYP3A-mediated drug-drug interactions. We recently have a few cases where the Investigational Drug in nature is the substrate of CYP3A as well as PGP and it also a

time dependent even […] CYP3A. So this is relatively complicated. And you probably will have a strong inhibitor study, drug interaction study. We're destroying human or maybe modularized both pathways meaning CYP3A and PBPK, and on the other hand is running up modulate both pathways through CYP3Aand PBPK. Now, we go to […] I only have one or two studies. Now the drug, is also a time dependent and given an inducer, so potentially can modulate the PK of itself, and we know that there are many inhibitors and inducers themselves are substrate of CYP3A. So the investigational product can potentially impact the PK of the inhibitor as well as the inducer. So this is relatively complex drug-druginteraction and is how are we going to […] is this. So again, in the show the medication or drug is a CYP3A, PDP CYP3A, CYP3A TDI and inducer? Here is our apparent thinking. The first question we would ask whether PGP plays a role in the drugs absorption, distribution, metabolism and elimination significance of it because while more transporters are relatively complicated. So, we want eliminated that early phase. If that, if we know that PGP does not play an important role in drugs absorption, distribution, metabolism elimination, then we need to provide justification. And then the second question we ask is whether the medication or drug is a sensitive CYP3A substrate, and if it is, there enough single dose or multiple dose PK studies and at multiple dose levels that will allow us to characterize the CYP3A modulation factor of Investigational Drug. So if no, at current stage, we want to evaluate the perpetrator effect of the master vision or drug, of extensive CYP3A substrate with […] study, primarily due to our lack of in-vitro extrapolation experiences with time-dependent innovation, and then we would incorporate all these known mechanisms in our PBPK model. If the drug is PGP substrate and we know that PGP plays an important role in drugs absorption, distribution, metabolism and elimination, we asked to incorporate PGP in the substrate model and then evaluate the effect of PGP. Now, this is a complex situation there are a lot of uncertainties in the parameters and what are the expected chance of sensitivity analysis to explore the […] associated with the uncertainties in key parameters. There are a few examples that we recently observed. This is not an all-inclusive list but as you can see just on top of my head I can list these examples where the drug it's a CYP3A substrate as well as moderator. There are both CYP3A inhibitors as well as a drug CYP3A substrate inducer, and majority of this studies they have a dedicated DDI study with a sensitive substrate, which is we determine and for a couple of cases where we partially accepted model where for what for a draft, the case was about that the acceptance part was not related to the drugs modulating effect on the sensitive CYP3A substrate but really it'srelated to his induction potential as a CYP3A substrate. While for a definite it's not a sensitive CYP3A substrate. However, due to the lack of in-vitro enable correlation for time

dependent in either a desolate interrupter interaction study to characterize the TI effect, we accepted substrate model as the as the country from CYP3A to its on metabolism is only 20%. So we can sit there even though at one having had may have impact on CYP3A substrate, it won't have much impact on itself in terms of PK. We also observed a few cases where the medication or drug is a substrate and PGP substrate. Here like less than one product where there was a community interaction study, and PGP was not incorporated in the original model, but it was incorporated into the model during the review cycle in response to our information request, and all these cases examples can be found via […] FDA. The second case is about induction. In many submissions, this our current experience we have seen that defending DDI studies were often under predicted. Here just listing a few case examples, but there are more lively and it is consistent with the literature course where CYP3A substrate maximum induction potential continues to be refined to match the observed director of interaction studies. So after seeing all these […] studies, we started to see what repentance that is really, if you think from all the perspective what does the study with refunding informed model? Well, I would say the strong inducer […] study alone provides limited information. What I think about is if you have a CYP3A substrate, you'll observe 80% decrease in a use the chances are high that we probably proposed will propose the word use. Now we started worrying about the fact of the matter inducer. So however, the strong the DDI study with struggling […], it doesn't really tell much when you started building your model inductions model. So our current thinking is effects a modern inducers making more rather than whether drug it is a sensitive substrate, especially if you want to propose dose adjustment for a moderate inducer. Now, there are some additional thoughts on those modification when the drug is called a minister with an inducer, especially the absorption they sometimes overlook the absorption issue because you want to increase the dose the way you coordinate your drug with a moderate induce and maybe sometimes twice, whether the dose that you are proposing has been studied in your various trials, and whether the drug has low side of it in the way you increase those that may, the son of a limited absorption may come and play a role. So those are additional thoughts, they want that to consider. The other consideration is about the safety and efficacy profiles of your major metabolites because with inducer with inducer sometimes was the, the metabolite of exposure will increase, whether it's still within the limit of safety profile, that's something you want to consider. And the third case example is about metabolite. When should I include metabolites in the model? I understand that metabolites can be very, very intensive in terms of modeling work. They're like new molecular entities that had to study all the […] option but DME properties in […] also it's a lot of work, I understand. But sometimes when you have to think about

metabolize, our proposed the current thinking is first we have to follow the mutual Drucker interaction greatness where it laid out when You should study the metabolite as the substrate as well as a perpetrator. So you would follow that, and then .And then there are some additional considerations that we've we want to, to discuss over here. Oftentime, metabolized, metabolites have longer half-life. So they accumulate a steady state, what you observe under single state under, single dose, whether it will represent the extraordinary metaboliteand steady state. And a lot of times, we'll have to think additional layer, which is the exposure of both active and inactive metabolites under the eyes scenarios where the exposure of those active metabolites as well as inactive metabolites may change different directions. So for example, the for another TDI scenario, that's a chain exposure to major metabolites cost safety concerns. Major metabolites can be effective in under TDI scenarios does change in exposure to active metabolites, cost safety and advocacy concerns from a dose adjustment perspective, especially if you wanted to propose dose adjustment for any TDI scenarios. After considering all these factors, you're making decision whether you want to be metabolites. We had a few cases where the drug or the metabolites both as substrate as well as perpetrator in check, and it was recently approved and there was an active metabolite M5 accumulated at steady state and contribute significantly to efficacy. M5 was not incorporated during the original model. When recommending their reviews and I called the review team because either they contributed to the efficacy so ask the sponsor or the applicant to incorporate M5 in the PBPK during the review cycle. The second case […] and there was an […] metabolite, M9, and during the review cycle, the review team had a concern that the exposure to M5 will increase significantly when the drug was called strong inducer, so M9 was incorporated during the review cycle for its assessment, and by comparing the so called and predicted exposure to the safety margin coming from the non-clinical studies, and there was another drug recently approved which is Cannabidiol where the […] highest assessment is for ongoing for two major metabolites. So, of course, if you want to predict, to predict the perpetrator effect of the drug, you cannot ignore the major metabolites because they are going to be generated in your system. Therefore, our assessment was PBPK was pending in-vitro DDI assessment for the two major metabolites. In case I'm going to talk about specific populations. This is my very topic because we care about every patient and also because we don't really know it's not like DDI scenario, where we know how to let it anymore. Although the current status of all this type of simulations is that became data I needed for more validation. So I think this is a great place where we can potentially implement the risk […]. Furthermore, we discussed in the morning. I will give you a few examples where the PBPK model can describe observed the PK in this different populations in pediatrics.

We were, there were many more examples, where the model incorporated their ability to attach meaning also incorporated and maybe administrate absorption models, and the model where I was able to describe observed became this specific population. For elderly population, we had an example where the model incorporated matching age and the model was able to describe the PK observed the PK. We had quite a few cases where the PBPK model incorporated parameter changes in disease populations such as protein levels, and the models were able to describe the observed the PK. For hepatic integrated impairment studies for us, the populations also had a couple of cases where the model, where the models were able to describe observed became those specific population. But as you heard in the morning that we need more examples as we do for the drug-drug interaction cases. So, in terms of how to move forward in this specific population became prediction that this is what our current thinking is. Maybe we can do step by step approach combined in modeling approach with limited studies. Now, I hope that this type of model can also inform in terms of how you desire study, so that we can do this, the trial smartly and back to feed a model. There are also system parameters that we need to understand, but some of those parameters are difficult to measure. How are we going to get those parameters right? We have many cases in substrate models. Maybe we should look at them systems is technically group similar compounds in groups similar populations but may ask how similar you'll considers in advance. That's more detailed discussions are needed. The third, the fifth case example is where are we with transporters. I laid out here the focuses of our kind of review. Just provide a little bit of detail of how we review when there are transporters mediated drug-drug interaction or transporter-related drug substrate models. Our primary review is focusing on both the substrate models as well as the perpetratemodels. So for substrate models, we will we have accumulated enough knowledge to characterize the substrate models relevant to the transporter of interest and intended model is prime all available PK as well as pediatric studies. Our review on, our focus on the perpetrator models is considered more qualitative and quantitative meaning because there is a lack of in-vitro in vivo correlation for especially the bigger mission constant. There are a few cases in the submissions where the PBPK models involves transporters. Now here there are two examples, smeprevir and letermovir, where they view transporter-related drug disposition in the model, but the model was meaning used to describe the PK difference study observed in different populations. So we would consider those type of application as exploratory. There are more cases where investigational drug is the perpetrator. As I mentioned, our review from […] substrate model as well as perpetuator model for optimum mates on training related DDI studies. Our current review for the metformin model is that the metformin model cannot

really capture all the recording drug-drug interaction especially high higher dose level for example 500 milligram. Our current review for PBPK mediated drug-drug interaction for example, direct interaction for example, […] we consider the model is more qualitative than quantitative because we know that the drugs were mediated PGPU-related drug-drug interaction. However, due to the lack of in-vitro in vivo correlation, especially for KI […], we don't know the exact magnitude of increasing for example, Digoxin exposure. So, in that case, we recommended staggered dosing, but if you think about this, if we know that how much the drop that how much it just exposure is going to be increased quantitatively, we will provide a different recommendation rather than recommending standard dosing would probably more recommended dose adjustment, which is mass confusion from patient perspective. Third cases out OATP1B1/3 inhibitors, where we recently reviewed. Our apparent evaluation the substrate […] study cannot capture of reported drug-drug interaction especially DDI […] story. So those are the five examples just summarize. You've seen that PBPK analysis become […] development and also submissions. PBPK can be complex and challenging depending on how many pathway signed up, how many intended use in our proposed that you want reported. We want collaborative effort of […] regulators, independent researchers, platform developers to achieve the goals of successful PBPK analysis. There are a lot of people who are working really hard that behind the size that, I'm afraid that if I put everybody's name it will be he wants not like to stand the work. Our work group organizing committee members especially Lauren and we have dedicated members working outside of the room, our PBPK team members. We simply have four members currently, deep division pharmacometrics and Office of Clinical Pharmacology, measurement, as well as colleagues also like to send an advocate and review teams who contributed odd case examples, and that’s all.

Shiew Mei Huang: Thanks, Susie. Now I'd like to introduce the second speaker. Dr. Nina Isoherranen. She's a professor and chair and I'd like to emphasize […], Chair of the Department of Pharmaceutic School of Pharmacy at the University of Washington. She has done a lot of research, very prolific in the publications more than 100 including publications in involved with PBPK. She's associate editor for a couple of journals, drug metabolism and disposition, and also ASCPT Journal, The Clinical and Translational Science. So she received many scientific awards, the young investigators award both […]. Nina has spent two months with us last year, and she has many stimulating discussions, ideas about PBPK. Nina?

Nina Isoherranen: Thank you Shiew Mei for the introduction, and thank you for the organizers for having me here. It's really my pleasure to be here. So I want to before I run out of time, make some acknowledgments. I want to acknowledge Weize Huang, who was a graduate student in my […] and host research and thesis work on maybe going to be presenting today most of the data I'm going to […] shows recent graduate research. So I want to acknowledge the funding from the NIH and to endowments from the University of Washington that have supported this work and enabled the completion of it. And if you are interested in looking at some of the data that I'm going to be presenting today, more in depth, I've included the three references here that you will be able to find most of the data. And so I want to start with just sort of to have in the back of our minds the concept of Fit-for-purpose modeling, and so the academicians view or political purpose model. So I think when we talk about the questions, I think one other way to look at that is because does the PBPK model help us to make decisions and ultimately because of the amount of resources that we put into the model development? Does the PBPK model help us make decisions that we would not be able to make without cannot? It is truly helpful for the purpose that we intended or alternative alternatively for an academician. The other question is does the PBPK model help us generate hypotheses or drive hypothesis generation that we can then go test those hypotheses in experiments and clinical studies. And I think all of the model should really help in understanding the system and understanding why drug disposition looks the way that it does, and I should have borrowed a statement here from the field of economics in the bottom of the last slide, while asking the question of is the model that we use and simply the best available or is truly adequate for the purpose of interest?Maybe even if the model is the very best that we currently have, that doesn't necessarily mean that it's good enough. And the other way around something is not necessarily the best possible today with all my tuning, it might still be good enough. So simplified models might just be good enough. So I want to start with showing the simulation that seemed to go really wrong. And the purpose of this simulation exercise was actually to model

methamphetamine and amphetamine disposition in pregnant women and maternal fetal transfer method of amphetamine and we're sort of still on the path of trying to reach that goal. And what we saw is this is showing a simulation of my amphetaminein the middle as a metabolite of methamphetamine. And what we show in this simulation is that when we modeled theamphetamine as a metabolite of methamphetamine, we saw this very curious spike in the beginning of the metabolite profile. And we looked extensively in published literature for all metabolite PK, but in this case, on the right, it shows the amphetamine PK as a metabolite of methamphetamine. We can't find actual real life data that would show such a spike for metabolite profile. So the question is, what is wrong with this PBPK came out? Is it like we're talking about earlier today, is it the software or the modeling the algorithm they solving it in the background? Well, the first question is, that's the first option that we thought something is not right in the simulation. So you restart the program, you see the same exact spike. You restart the computer, you see the exact same spike. You rebuilt the entire model from scratch and you don't see the same exact spot. So we came to the conclusion, it probably isn't some local movement that they call, you know, the system crashed and that's why we're seeing something strange it is probably something really wrong. So the question is, is this the structural model? Or is it the drug model that somehow is wrong. So what we found is, we had a feeling that this could be a distribution issue, because depending on that spike, the actual AUC of this curve is not really affected by the spike. So this is really appears to be some kind of a distribution phenomenon. And what we did is we started changing the parent drugs KP to the liver. So this is changing the KP from 3.3 to 13 for methamphetamine, and that has a fairly significant impact on the shape of the metabolite curve. And what you see here is that by optimizing the KP value […], keeping the clearance first, we can actually go from this spike to someone with no spike. Now the question here is, can we accept this model? It starts looking like reality, but doesn't look like reality for the wrong reasons. And I want to really emphasize this uncertainty of the Kp values that were used in complex PBPK models and the degrees of freedom that we introduce in the models by PBPK models. So it's very common practice and if you publish in this area, you will often get comments from reviewers on the fact that you should use predicted PBPK values by being very broad and cited projects the role and method in PBPK models and that's what our initial Kp values indeed way work. Now what I want to emphasize here I picked five tissues that we have predicted […] enrollment equation predicted Kp values. The left post can show us these values predicted based on the original publications, but taking some of the tissue compositions herefrom humans. So we don't have tissue competition for all the tissues. But this is this was called human hybrid. Coming back to the issue that

was mentioned earlier, that for a lot of these things, when you read broaden the literature, you'll find the background equations and you can do this on a spreadsheet. The next time there shows the same exact prediction down using commercial software. And why I'm presenting this is to show our confidence in this predictive numbers because you see that even when we use the same reference text, we think we're using the same model we actually arrive at the different numbers. And then finally, the most, right most common shows the observed had data for this Kp values. So in this case, for methamphetamine, there is a PET study where we can look at the Kp values and you see that we are quite far off up to almost 20 full raw in the predicted versus the observed. And this tells you that really we have fairly low confidence on the predicted Kp values. But we can probably from the human PET study think there's some fairly reliable. […]. Now, we use those observed Kp values for this modeling exercise, what we see is that the metabolite curve now loses that strange spike and actually looks very similar to what is the observed of data. So we use observed Kp values instead of predicted, it all looks good. And I can tell you that having started with the observed Kp values, probably the rest of this talk wouldn't exist because we would have never looked at. But the questions here as that now seems, despite points away, and the AUC and the clearance looked right. Is this model good enough? Is it fit for the purpose that we are aiming for meaning? Is it fit for predicting methamphetamine clearest and disposition of amphetamine in pregnant women? The other question is, does it replicate the observed data for the wrong reasons? It looks right, but it's the backdrop still wrong. And then finally, is the correct conclusion from this exercise that the strange hike that we saw was because of the drug one being wrong. Is that the conclusion equation […]? And those are all possible, is possible to answer all of these? Yes. But we continue from here to assess the other alternative hypothesis, which is that maybe it's the structural model that needs reassessment the true model and not just the simulation. And what we realized because we're thinking about this in the context of distribution, that mostPBPK models actually, I would say that 99% of the PBPK models out there sample work from the central data essentially, or what is analogous physiologically to the right atrium actually where they inferior and superior in vena cava merge. So our sampling side the concentrations were simulating are actually right a concentrations. And if you back 20-30 years of pharmacokinetics, we used to, we actually developed from looking at the theory based on arterial concentrations, and arterial sum. However, our observed data is almost always from a peripheral sampling side, or rather than from the arm vein and when we compare PBPK simulation data, we compare essentially right atrium concentrations that are similar to our theory as concentrations to observe our data. And why might this banner, what I was showing

here is Ketamine IVinfusion. The red dots are the observed arterial concentrations and they are blue dots are observed venous concentrations. And you see the true observed differences in arterial venous concentrations exists. And what we were wondering is could this where metabolite behavior actually be due to this discrepancy in the sampling side for the observed and predictively data. And what you see, we went and developed an army of sampling sites, which is shown on the rightthat allows us to simultaneously sample both the arterial and the venous concentrations, and that's the blue line on the red line thereso we essentially verified the structural model for simulating arterial venous disease and can capture it by simulations. So the question is now how this impact our metabolites innovation, and that's shown here. In fact, what we found is that that very peculiar spike in the metabolite profile is due to the fact that we are sampling from the right page, and not from the arm vein. So what you see here is a simulation red line from the central sampling site and the blue line from the arm vein and clearly see that that spike is due to a sampling size. So what we've hypothesized from here is that actually optimizing the Models when the sampling in the model for the central site. But comparing that to an arm vein observed concentration may actually have an impact on the quality of the model, whether it's feasible purpose and how well it can be extrapolated to different things. And it's very difficult to assess this in terms of figuring out which ones are relevant parameters.Different homeowners might have different sensitivities that caused the model to be either people purpose or not. And then the question, how does this affect static scenario? So when we start talking about extrapolating a model advanced studied scenarios, I wanted to show this example that was published in Nature in 2004. And what this paper shows is a linear analysis of the female and male sprinters in the two lives and how the time for the hundred meters sprint has gotten shorter and shorter, as the function of time and the observed data clearly fits a linear regression model for the time from 1916 to about 2000. Now, what the author said is they extrapolated this further into the future, and predicted the 2156 Olympics, women will run faster than men at the 100-meter sprint. And if you want to go, you can go and read in Nature, the extensive commentary for this, but I think the best part of it was the comments on the raised on 2636, because if you extrapolate these lines all the way to 2636, at that year, the 100 meters is going to be running negative talk on and this really tells you something about the assumptions when you extrapolate a model, that these nice linear regression initially, but if you assume that those mathematical relationship hold true through your extrapolation, you meant it may end up somewhere that you wouldn't want to be and I've taken the classic quotation from George Box here about the science. Since all models are wrong, the science must be alert to what is important to the wrong. And that we make

tentative assumptions about the real world, which we know are false, but which we believe may be useful, none of us. And I think we need to remember this would be the PBPK model that what he said already in 1976, that we make assumptions about the real world which we know are false, that we should remember that we should know what is false in our lives. So now how this affects the extrapolation in terms of the arterial venous differences. What we did is we took bottle fentanyl as an example, and that shouldn't be one reason for this is because we wanted to look at arterial venous differences are relevant for other routes of administration except just intravenous. And what you see here is buccal fentanyl is partially absorbed from the GI lumen and partially absorbed through the buccal mucosa and you see the observed data there for the buccal fentanyl in the arterial side of the red dots and in the venous side of the blue dots, and then our simulated fentanyl concentration of the two sides of the lives. And what we see is that essentially, we feel pretty good about our fentanyl model validated to multiple IV sites, but I feel the best one is the simultaneous verification against the arterial venous samples. So the question now is, can we take this model that we feel is pretty good, and extrapolated to a new formulation of fentanyl for example. How does this side affect the works to collection and what I'm showing here is the physical purpose. So in the left, we show the arm vein simulation and ar vein sampling, and you see KA values for the buccal and […], one per hour. And then the next panel to the right shows the observed arm vein data and on the red line, the simulated central site. So that would be our classic PBPK model simulation where we sample from the central side of the right atrium […] and what you see is most of us as we're developing a model would look at that and say the Cmax is way on the side of the range and something is not right with this model because we're not capturing the shape of the curve correct. What we can do is take the KA values that we often have very low confidence, because they're very difficult to actually truly measure in any […] system and optimize the KA values both with the buccal and the […], so that now our observed data and simulation central side shown in the red line at the very right overlap. The gray dotted line and that curve shows where the arm vein sampling would be in this case. And what this shows is we're essentially introducing the incorrect KA value here in order to make our central site look like the arm vein. Does this now impact what should happen if we simulate a new formulation. And that's shown here. So in the top of the two models, as I showed in the previous slide, on the left is what I would call the correct model, meaning that the arm vein overlaps with the arm vein, and the central side of sort of off, and then on the right is the optimized case for the central side, face the armpit and you could say that if we simulate an unknown scenario, the error in the sampling site should cancel out we should not worry about this. But in fact, it does not cancel out. If you

look at the left hand side, the fentanyl concentration would predict with the correct model meaning this consistent sampling side we predict only a 40% change and you see that. However, when we take the optimized model, then the arm vein samples for the central side was optimized to reflect the arm vein while you predict is 120% of change in the Cmax, and the point of the simulation is really to show that seemingly important than the minor model optimization can have a major impact on predictions or arm studies scenarios. And I kind of made this analogous to the Lorenz's butterfly effect of how the butterfly flapping his wing and the other side of the globe is going to affect what's happening here. We wouldn't really think that the minor adjustment in a the KA like we did this […] water will have a major impact. But in fact, if you start running these simulations, if might have a major impact. And the question here again, signing from George Box, that 13 years later is that the practical question is how long does the model has to be to not be used. And I wonder if we just spent the last few minutes in talking about that issue of the confidence in the model and the degrees of freedom and I want to remind everybody when I talk about him all people always was why do you need so many, so many compartments. They think many times we forget how many compartments we really have the PBPK box. There's usually at least 14 compartments. And each one of these compartments have multiple parameters associated with them or quad flow, organ volume distribution, clearancy, […] clearances, KPs so forth. So oftentimes, we have at least 70 degrees of freedom, and when we start talking about sensitivity analysis that results in a global sensitivity analysis that 10 to 70 similar simulations, which you need that the best supercomputers in the world to actually do them. So typically, we get to some more local sensitivity analysis, but it becomes very, very difficult to pick the right combination of parameters without prior knowledge to really figure out what are the truly sensitive parameters in them. And I think this is something that is a major question, how do we statistically start assessing the quality of the models and their sensitivity? And the biggest question here is that oftentimes multiple parameters are interdependent. So if you optimize one of them, you need to optimize another one to actually get to the final answer, and I'm going to illustrate that with the kidney model here. So coming back to my methamphetamine and amphetamine example. When we started working on this project, we remembered the classic work from Malcolm Rowland about the pH dependent adrenal clearance. And what is shown here on the left is from his papers showing the effect of urinary excretion of methamphetamine when the urine is acidic, or basic or the urine pH is sort of neutral, uncontrolled. And you see that there is the major changes in the pharmacokinetics and the clearance based on urine Ph. And what we needed to do is develop a model to allow To simulate this, but when you start thinking about the renal clearance, it's

a real challenge because in terms of the modeling and looking at the legal data, the tubular secretion, and the passive reabsorption are sort of interdependent parameters from looking at in vivo data, you cannot differentiate them from one another. So if you have a drug, and as we will have sufficient permeability to have the reabsorption, this becomes a real problem because you have to adjust onein order to compensate for the other. So in order to get at this, we figured we have to have really good confidence on the passive reabsorption clearance in order to be able to address what fraction of methamphetamine is actively secreted. And to do this, we developed a mechanistic kidney model that is fully based on true kidney physiology. And we allowed both the flow and the pH changes in this model so that we can simulate like the various pH dependent currencies. And what you see here in the left is the verification of the model with the drugs that do not have active secretion, so neutral models that we could basically go and verify that the passive permeability data is correct. And then because of that, we could go further and actually get the confidence in the active secretion of the methamphetamine and amphetamine data. And that's what I'm showing here on the on the slide is the application of the mechanistic kidney model to predict the urine pH effect and on amphetamine disposition. And what we have in this model is the amphetamine passive reabsorption as well as the active secretion of amphetamine by OCTs and based could be active, and what you see is the three lines there. The green line, in this case is the outline urine. So the clearance is very low. Then we have the acidic urine in the blue line. and the red is the uncontrolled. And downstairs, showed two individual subjects for the observed data. And what you see is that we can fairly well using this model predict their therapy and the disposition in various different urine Ph. And what I really want to emphasize here is also the massive impact that urine pH can have for these types of compounds on the overall exposure. This essentially is a sensitive substrate in terms of just the urine pH changes and changes and real clarity. Now, one of the points that I want to make here is that we have two subjects that we predicted, we get fairly close to both of them in terms of our simulation, but when we simulate something, we can't necessarily predict the probability of observing any one of these things without having a really good understanding of the parameter distribution background, so I think we should take some some Thinking on also the statistics on how what's the likelihood that will predict what we observe and within what kind of range. So with that, I want to get to my conclusions. And I think the first point that I would like to make is that the KP value should actually be experimentally determine. We should start looking at animal data on what is true tissue distribution if we are simulating things like Cmax or actual time courses of drugs, and ideally that the assessed should be converted with IV drugs and data. I think the sampling side in thePBPK case should be matched to the sampling

side of the experimental studies or vice versa. Ideally, you would have observed data and our theory on the data side so that you could simulate both. I think we should think about the complexity needed in the PBPK models and aim for personality and that will allow to identify the components in the model that are importantto the ground.I think we need some statistical methods that account for the increased degrees of freedom. Because obviously, the more parameters of compartments the yet, the better the fit is going to be. Just like four compartment model typically fits better than one compartment model of PBPK data. So we need to think about how do we assess the actual increased information that we get from more complex model. And then finally, I want to sort of emphasize this issue about extrapolation that when we extrapolate on studying scenarios, we do make the implicit assumption that the same mathematical relationships apply in the extrapolation as what we had in a tribulation. And I think that's something that, you know, is addressable, but I think we need to give some thought for. Thank you

Shiew Mei Huang: Thank you so much Nina. Now, I would like to introduce the third speaker and the last one for our session, Dr. Yang from Yanson. H is the director and research fellow in drug metabolism and pharmacokenitics. He has extensive PBPK experience for more than 10 years. He has worked on the prediction of PK, doctor interactions, organ impairment; and he has worked from retrospectively looking at the model to close […] simulate clinical DDI trials and also to address regulatory questions, and to wave of clinical studies. Dr. Yang is the one of the sue individuals we have invited to OCP many years when Fidel is here to share his extensive experience with PBPK.

Dr. Yuching Yang: Thank you Shiew Mei for the nice introduction. I want to also thank the […] for inviting me and given the opportunity to present some of the work that I have been doing to use PBPK simulations to address […]. This slide gives an overview of young's lost 8 years […]. What you seen over the years the main focusing of enzyme-based infection but in more recent reviews we also have basic knowledge especially relating to update […] intervals with everything inside […] were also going to be getting in back. Also, in recent years we see more application of indication […] central products with things […]. […]. The gauge optimal which I will discuss today is divutinib. It's one of the early we tackled but I think for now 6 years today of the […] of approval is the next study we evaluated motor-based information […]. Before I jump into the gauge into […]. So, we will always thought on the specific question and then we tried to internally develop deep scientific expertise in the […] which are used to generate […]. We also make sure we're aware of the equations […]. And also […]. When we talked about identification of system components we tried to bring out the […]. When we talked about fair indication of the PMO. We try to use all relevant clinical […]. And then the most important form is like[…] factorization that most would be a very risky so we always have to be in a rational approach and always experiment […]. And the lost option [coughing].

Speaker: Sorry I pause a few microphone.

Dr. Yuching Yang: So, the lost part that we always have to be mindful of compound that we're working on and for which population is this, and how precise the stimulation have to be without clinical compound. So, there is no one size fits all for certain navigation always depend on those specific compound and the specific indication.

Christopher Joneckis: And zoom on ibrutinib?

Dr. Yuching Yang: It was first approved in 2013 for lymphocytic lymphoma. Since then […] has been approved and also recently showing both disease. When we zoom in on the […] unusual compound is a higher compound. It's eliminated by metabolism […] the major enzyme. It is completely absorb and it's showing high percentage viability. So, if you receive this is a compound which may be a victim of […]. When we zoom in on the specific questions where we […] examination. First of all can we use to relieve the effect of strong […] given that they have an observed TDI study with a strong critical subject. The second define to something similar but […] in users. And the third question was can we actually done most predictive effect of citrate perpetrators in […] subjects because we know that patients who mainly taking this drug in a normal setting and that involves question was to predict some impairment. Now, to be able them to see if we can rely the effectiveness in most addressing these specific questions we always try to build up a database internally to still evaluate predictive performance is so that we can use this as a reference to see if we can use PUK to this address these questions. So, first question regarding action stimulations what you see less is predictions of drug interactions without verification moles with the clinical DDI study. And on the right you then see if you have performed the critical DDI study and you are…verifying the […] and then using that verified mold to lift other whether the infections then you see specifically in the context if very correlation between the stimulated extended bladder infection. So, specifically, for this case example and this gave us confidence that if we would have DDI study with strong indicative we could actually predict the effect of […]. Then, specifically, the relief with them to no faucets of subject so I show the up to the effect and then depending what's the underlying mechanism of that food effective it can have effect […]. So, if you just increase it the faction absorbed it would not expect the different extent […] to get to the best possible predictions because like you saw on the previous slides has a lot of uncertain parameters so the more confidence you have it can always guide you if you see mismatch in predictions or reach […]. So, you see on prediction of clearance value on the left you see the first generation has more reasonable you have where you see more predictive clearance from yesterday and reserve…With the inquiry generate that includes genius value in predictive the key prediction of POE so that lead us then to also specifically verification with model stricture and what you see on this slide with comparison with the third model is urgent acute model. There are three different models which your intrinsic together with […] that involves the clearance. And what you see is that for weltered base model especially if you go to high […]

clearance. Whereas for no clearance actually the […]. So, perspective there again some context on where we have confidence in roster based models for which type of drugs we don't have given the confidence in […]. At that point in time […] base specifically for dynamic agents roster based. So, what we then did is rescale up the intrinsic […] that gave us clearance and then we evaluate which intrinsic well stuck model would us […] so this was a […] to address a certain medication in […]. Then, this slide show you the predictions of ketoconazole your drug interaction on the YXC you see the extent of interaction which would predict on the X axis […] stimulate impulse in rents you see the adults from […]. So, what you see is that the model is able to capture the […] without the perpetrator and also the ability of that would also extent of the interaction and that seems to be captured nicely. So, that gave us strong able to create […] therapy. It was captured. So, then in the next phase we have verified […] which were redefine based on […] and then you are going to predict the effect […] stimulations […]. Now, specifically for the subjects the exercise showed if we just incorporate the effect of […] to the liver into the model that we came…that the model could stimulate the extent of […]. So, that's the mechanism which is incorporate models who don't need an additional effect of food and […] to capture the food effects and if we then stimulate the effect of produce […] ketoconazole therefore increasing the indicative […] which you saw in the subjects it gave the ketoconazole between 24 to 34 interaction who has in compromising […]. We refer back to the impression […] this morning like differences between […]. This is also an example if you for this type trial […] to clear difference the extent of infection before can be […]. In interest of […] specifically the direct response […] some of the language for […] dose of 560 mg was improved and then if you look into the label on […] reduction of 560 […] for in use is also stimulation more induced difference and strong […]. Specifically informed about insufficiency in line with our internal […] that can be the initial label as supposed just insufficient date […] medications. So, in the initial USPI so there was no mentioning of the effective interaction in subject although what you can see is with the full dose reduction with efficient one would stimulate that effect with model for four folds those reduction should still give you the definite exposure which should be equal to 560 mg exposure in […]. Now, what really interesting is then that now 6 years later, actually some of these is unknown scenarios which were informed in the stimulation that there are actually have much more sort of date than we have in 2013. So, left is the study we conducted in […] patients where there is…if we dose 560 mg of […] the dose reduction like mentioned in the label where used to 40 mg […] ketoconazole we did end up with similar exposure what this trial shows […] is that indeed the reduction of 40 mg […] results in similar exposure as the 560 mg patients also a very recent publication in subject with the interaction

with itraconazole now so […] DDI study in […] subject […]. If you knew now the study with strong inhibitor ketoconazole […] increase in HC and increase […]. If you knew now the study with a strong C3 inhibitor itraconazole against ketoconazole to be more actually see that the […] also with the simulations of the interaction. What about the impairments of position was that could not be used […]. So, if we look at this slide we resume specifically on the simulations of the extent of exposure increase and different population of impairment first with the observed data that we consistently see […] over predictions so at the start we have define is that if you would use it for to inform the label that there is a risk that would involve to use subjects with […] so we are concern most […]. However, I do want to highlight that since 2012 so progress has been made in our understanding of physiology in […] neurologist. It shows in the middle now you see of the more recent data we have and comparing the examinations first observed we received medical relation […] as well as the data set when we referred from the IQ consultation. Specifically, child […] there is a very […]signs of impairment first review of […] although in child group B and child group C there are still cases of over prediction no case […]. Now, if we then use a more recent version that was […] and then again stimulate the extent of impairment of […] and you see now a more recent versions of the virtual impairment that actually no25:29]w without asking question […]. And this specifically has […] something is […] this generation will […]. So, to summarize I think I showed within the gauge is on some questions where we had a very […] and also cases where we have to move […] six years. Actually, we know that the labeling […] was actually informed by […] specifically also that questions where we preferred […] data that actually confirmed that the concern […]. So, acknowledgments if the […] also project involves colleagues which have been working on the case […]. Also, what is crucial is that we have the group sign dialogue between industries especially if you want to address […] and also the interactions with the software always helps in keeping what the perspective is and […].

[Applause]

Shiew Mei Huang: Thank you so much you give us some time for panel discussion.

Colleen Kuemmel: So, we have here Suzy given the several cases from the FDR review and the clinical pharmacologic area and were there were written commitments with the sponsor and she pointed out the […] would review. To show a couple examples pointed out some time may be made and models may not be predicted if you are fit for to grown

reasons and we heard a very presentation of 2013 or thinkin 2019 for the models. Because of increase on the standing seasonal allergy and perhaps the quality data of drug model and the system parameters. So, I would like to start to ask one question of our encouraged individuals to […]limited of time. So, we have an impairment as the sample what would you think that will be helpful as far as drug parameters, system parameters or model? What are the key information that's missing in most of the applications, only talk about the drug development not specific on research or the reviews that we have. May be e will start with Suzy. What parameter that you think we should have that often are missing which make the review very difficult and very challenging?

Sue Cole: […] the submissions that we have. Drug parameters should be well characterized your healthy system. System parameters there are a lot of certainties that we don't know. We […] is if though might thing that we care about. There are some histologic change in the liver for example the impairment subjects. How that is going to do prediction. Often time we see over friction which is consistent with the data that we fermented but many times we don't know how the solution as for reviewers we don't have time to figure out why. I would like to see sort of surrogates studies that we can indirectly inform prediction of having impairment settings but again how to discuss […] halfway for reason whether it's high clearance or low clearance drug it doesn't matter. As you have mentioned there are a lot of uncercenties and a lot of parameters in complex. I think we have the […]summer and […].

Shiew Mei Huang: So, I think that impairment was always frustrated to me and […] that the actual data that the index substrates that we have really really good understanding outside that impairment […]. It's very difficult to find index […]. The other thing that would be good […] impairment is also issues that I've seen in […]. So, you think often times we see […] critical and I'm not sure how well we really stand changes in absorption rate […].

Christopher Joneckis: You first people […] so I think is a very complicated issue deals with […] enzymes […]. It all changes at the same time and especially in severe […]. So the date I showed today has has become very healthy subject population […] molds which are highly towards the […]. I think the future is really trying to peace out […]. We then also try to identify some of the case with […]. I think base on the data there still some enzymes where there is some question marks […] with the reasonable a little […]. And also what we have noticed specifically […]

so I think one of the factors that might be missing is that in for compounds which needs […] than severe lymphatic impairment that there is also an effect all aspects in the GI tract and this absorption and this also needing to do this home prediction when we compared the ratios but may […] that the enzyme […].

Sue Cole: So […]. Please state your name and organization. […]. I'm surprised that you guys made a statement that all […] will be measured that we credit but we would increase significantly cause […] and I read that the existing […]. Actually there are mental symptoms […] distribution. And for continuous itemization of surviving […]. We still lack of some compounds or volume distribution. One of the issues that is currently is lack of […] in problem distribution. I think you can easily see the predicted volume distribution is correct or not. And in our practice we often making the absence of […] and we try to predict and a few corrections in all distribution if necessary and if the corrections are the same for a close species or similar then we can compete […]. If not then we could have […].

Shiew Mei Huang: So, I think those like completely that the intravenous data should be there for every PBPK model or not? The one who reviews this packages. So, I completely agree with you that there should other data to fill […]. I completely disagree that the KUB experimental value to fine. I'm not talking about the PET scan study in humans I'm talking […] value in animals. You can use the same exact model whether you […]. In mathematical predict he KP in […] whatever you name it is not the at human except that you can take in composition in […] in species. So, I do believe that there is actually a lot of preclinical species distribution data the majority of composite are developed from radiolabel studies. And what I'm saying is for example […]. We have data that we could find the were measured in […] species. […] often that data is not published. It's not probably we don't manage but I think companies […] should have that data. I don't think it's major additional resource.

Sue Cole: So, these are noncommon in preclinical models in either the submission to helpful and strength in PBPK model […]. I don't know what's happening in internal industry based on our experience which are […] are called PBPK model. So, basically that means they need a lot of arguments together I guess one of the reasons is because […] are not accurate enough. A lot of times this is a the compartment that we are interesting for some […] we are getting those and in those

compartment I would give you a reasonable prediction for the purpose that you want. In keeping that is a part of one of predicted […].

Christopher Joneckis: Yes, […] in the absence of distribution should give you several compounds […] distribution. So, what we have found is that for the majority of the small molecules especially having your […] distribution and the […] distribution that created helps given the life. So, internally for most of the compounds who have at least have that […]. So, […] wet typically […] distributions rather that it is difficult for them to going through those exact treatments. So, […].

Dr. Yuching Yang: So, thank you for your involvement. I really […] so many questions in my mind. We have gone walking […]. And it was interesting to see that we change side […]. We also have […]. More so as we see these changes kind of […].

Sue Cole: So, in topic that I have mentioned that the […] but all the work that we gone now is seen […] were in simulation. Now, one of the big question we really has is what happens when we get […]. I don't think we have very good data for […] on GFR changes. I think getting a better understanding well. I think where the arterial venous difference […]. That could make a huge difference in the time course […]. So, I think there is endless amount of things to do in the pregnancy. What I showed you today probably…unless you're talking about maternal fetal ratios shouldn't impact […].

Shiew Mei Huang: Two more quick questions.

Dr. Yuching Yang: […]. If I'm using this PBPK and drug interaction is an interaction […]. So, we […]. So, in this case I wouldn't […].

Sue Cole: So, I have two answers. The first one is what […] toxicity that this is associated with CMax and CMax is going to be […].

[Inaudible]

Sue Cole: Depending on whether you know which is your pain and which is […]. If you don't have final data you don't […] question. Other things that

we didn't talk about […]. Then when you simulate the perpetrator […]. We are looking at the […]. Given it all they […] a huge impact with the actual concentration, the literacy of […]. And then the question is the PBPK model is your DDI written by the tympanic arterial even concentration or had an issue concentration which is actually […] concentration. So, I think there is a lot of questions of that what are we missing in the perpetrator concentrations, what is the affecting the sense of transport of some data when we are not actually stimulating an […] concentration. So, […] that certain perpetrator […] is let say an animal. You have to adjust it to one animal to see the correct DDI index […]. That is actually the cause we are looking at the wrong concentration of the perpetrator model. Now, […] an important question because the question is all we're doing on the future […]. We have two completely differently scientific questions […] and I think that's we are really comes to the point […]. I think AUC stimulation still very few perpetrators that fluctuate enough that there was truly […].

Shiew Mei Huang: Thank you […] on the question.

[Inaudible].

Sue Cole: And […] issues raised […] and I'm not sure if we realized just the amount of information that we could gather from […] of the disease […] disease is depression in the […]. I try to compete with the modeling […]. One of the issues that I have approaches is extremely difficult because of lack of information that I have and yet the dog is such a natural same way between the issues we develop in drugs […] that we should be developing on approaches using a stimulator given the […] with humans. When we use the clinical date, when we say […]may question to you is are you […] or are you truly […]. I think in terms of the approach to the KPs if it's […] that is a clinical data. If it happens with you food produce animals for that matter. I think it's just as good. I think the progression into the tissues we are […] are a rapid composition of the tissues just the same as human. I think […] offer to us in terms of understanding species things like that. But I think we could really make much more utility for examining with that data […] and you see a lot of model and make clinical adventure […] I think would be important.

Shiew Mei Huang: Thank you. This concludes our session, session three. Please come back at 3:00 for the session four. Thank you.

[Clapping].

Sue Cole: If you have questions please email them at […]. Thank you.

Lauren Milligan: Hey, everyone. Welcome back to Session 4. The panel of knowledge gaps in the PBPK. If I could have the panelists for Session 4, please come up to the table.And in the meantime, I'm going to introduce your moderator for Session 4, Dr. Stephen Hall. A special shout out to Dr. Hall as serving both as a moderator and the speaker. So thank you very much for your contributions today. Dr. Hall is a Senior Research Fellow at the Department of Drug Disposition at Eli Lilly where he develops new quantitative preclinical and clinical translational models and leads PBPK initiatives with an IQ. Previously Dr. Hall is a professor of complexity at University School of Medicine, an associate editor of drug metabolism and disposition from […] reviews and past board member, director member for ASCPT. Thank you. Dr. Hall.

Steve Hall: Thank you, Lauren. Okay, so we're, we're here at the final of the meeting, and we have plenty of time for your questions and comments. And you probably see from the program, we're going to read it out to you so that you really get the gist of what we're about in the final section. It says what are the most pressing and high tech scientifically technical challenges in application of biological and physiological challenges need to be addressed to allow the application of people became special populations, panelists will identify common themes, challenges and strategies to move the signs of PBPK forward. So that's that's really what this is about. Where would we like to be, say over the next decade, and how do we get there? And what are the things that perhaps we're getting away from trying to achieve those goals? So our first speaker is Iain Gardner. Iain is the head of translational PBPK science at Sim-Cyp and develops many of the tools that many of us use on a daily basis.

Iain Gardner: So thanks for the introduction, sir. In this short presentation, what we are asked to do is to really think about PBPK science is going, and some of the barriers that we're facing. And so what I tried to do is to summarize this, at least a vision of the future direction of PBPK science on one slide. And so, the areas where I think we're going to see increasingly use of PBPK models and scientific approaches over the next, say 10 years outlined here and so looking at ways we can build confidence for expanded application and predictive fate of drugs in special populations. So really looking at coupling PBPK models with detailed quantitative systems pharmacology models and also looking at the impact on pharmacological response. And thenways that we can integrate into became models with highly physical pharmacy models so that we can start to design formulations in silica and really start to move towards in-vitro extrapolation and using that to kind of guide virtual by equivalence. Obviously, looking at individualized in those situations by using the patient avatars and really pushing as much medicine forward. And then lastly, more technical thing that really

looking at robust analytical handling of observed data when we're trying to fit fairly complex models to data, and maybe really taking advantage of basing fitting models. What I want to do the next sort of three or four slides is just to kind of expand on each of those points and then finish with a slide outline and some of the challenges. So if we think first about special populations, there's already a framework and population really looking at to kind of highlight medical need for different populations. So you can see pregnancy, frailty, and also the amount of information that's available. We're already starting to make progress in these areas. So there are a number of publications where we've completed data that you need to describe the physiology changes in pregnant women publish those so that they're available for people to use, and obviously not just looking at pregnancy, but thinking further forward in some of the other horizons we might want to try and get to. And so also looking at PBPK levels, and starting to use them to perhaps look at some of the areas that are very difficult to study. And this case looking at lactation. So this is just one example. And that was published presentation at a conference. And obviously, we need to build the confidence in these models so that we can use a more routine. So moving on, we're going to see an increase in a couple PBPK models to constancy sex and pharmacology and quantitative systems, toxicology and safety models. And actually a lot of the work that we need a lot of the technology challenges that that we need to combine these models together have already been overcome. And we're starting to see applications from various groups on these types of modeling. So just a couple of examples here to accompany PBPK models to an immune response model or two quantitative systems toxicology described by […]. So again, not something that we're going to see more of in the future. And thinking about formulation design, the way that, you know, […] potentially can be used as, as if you're looking at the information about the compound, together with information about a […] that you can put in the formulation […]. So using the PBPK model with in-vitro data on how these different species interact, we can start to make predictions about what's going to happen in healthy subjects in patients. And really, in this case, trying to consider both between subjects and within the subject or let's say, obviously, they need to make a prediction with the concentrations and you can see with any particular formulation, optimize it virtually until you get a formulation that is meeting the objectives that we set out, and then use that formulation and contest it recovers. So again, sort of more diverse applications of PBPK models in two different places. And the last example I wanted to just touch upon is using virtual twin. So this is the idea of using personalized PBPK models and looking at patient avatars. And really what we're trying to do here is move from one size fits all babysitting three stratified those in and get them to really individualized […]. One of the challenges, obviously to be able to get a

prediction of the dice for an individual is in the semi covariance that that we know about any particular person. All of the things that's kind of been holding us back is being able to have an understanding of what the levels of the enzymes are for that particular person within the […] and obviously content […], so anything this is highly invasive. So what we started to see is copying PBPK models with non-invasive biomarkers. So in this case, they using things like an exercise of liquid biopsy to get a read of the levels of the enzymes that are going to be important in determining the donors. And then coupling that with PBPK models so you can start to it into an individualized post production.Obviously, once you have that prediction, then planning on how far in the future you want to go. You can have a robotic dispenser and various different types of delivery to the patient. But the idea really is to use PBPK model that's informed with individual information about the patient and these are to date for each patient, what place they should receive. Okay, so just to talk about the barriers there. So these are really some of the things that are unique to kind of tackle to be able to move forward. Obviously, further verification and qualification of the models is needed. And I generally use qualification as a term for talking about model validation, I guess is the way they would phrase it based on the discussions earlier today. I think one of the barriers is sometimes lack of quality data in the public domain. So again, that can be problematic. Obviously, there was sudden the scientific and technology, technological advances that are needed. So if you look at things like pharmaceutical workbench or […] and again, those are things that are going to come in the future, I think, as was discussed earlier in presentations talking about transport for abundance, and scaling the DDI prediction, we're starting to make progress. Again, data for transport such substrates is becoming available in humans so we can actually get organ concentrations from the packed data. Again, combining better techniques from in-vitro modeling starts to really make progress in the area of trends towards a GDPR prediction.I think that has to be a recognition ofthe use of kind of open science approaches to PBPK platform development. I felt that things always been never she try and publish the models and data in peer reviewed journals. And so far, if you look at the whole of the kind of SimCyp, it is a community there are 500 peer reviewed publications, looking at various aspects of PBPK modeling, which encompasses about 250 from the SimCyp Science Team to 300 from Consultative members and […], and obviously, not necessarily a barrier, but something I think that's really appreciated is the effort this needed to collate and curate and analyze the data that really underlines the pain levels isn't always fully appreciated. So that's all I was going to say about where I think some other kind of advances will come and some of the challenges and then […].

Steve Hall: Thank you, Iain. Next, we have GraceFraczkiewicz. Grace is currently a team leader at Simulation Studies team and Simulations Plus where she mentors and manages a team of scientists to provide a mechanism to the mechanistic, modeling, consulting services, pharmaceutical industry. Grace?

GraceFraczkiewicz: Good afternoon. So I'm going to focus on mostly needs of the several areas […] overdue in a special populations. When it comes to disease models, often we don't know the whole impact of the disease on the physiology. As a PBPK modelers, we tend to focus on systemic changes the caused by the disease that we can measure, and how these changes affect volume distribution and freedoms. And we tend to look at it as bangs and changes in specific organ. It became mostly affected by it affected by the disease. But often it doesn't, if the most accurate predictions in the disease population or if he keeps the typical predictions that early stages of the disease but not always a good predictions. She when the disease sees in is advanced state. One of the examples that I wrote here is a concert which is a complex disease and economically recovered successfully preventing cancer patients, which leads to specific cancer or early stages of the cancer. In advanced stages of the cancer, one model is so difficult to arrive at, and in this case, we when we look at the individual data for the subjects that we have in the data that we can see that the most, sometimes profound factors affecting observed plasma concentrations are on the absorption site. And we can predict some of these changes. We know that patient's history of the disease, the tried and true methods and oxygen surgeries and this kind of information can be typically updating all the plumbing, we've updated the combo to basically from below data. So instead of the challenge that we face, painting this kind of information that a […] about the disease of our other diseases code. When it comes to that, we are doing pretty well with BCS Class I and II compounds predicting that it would affect, but the BCS Class III and IV compounds did pose a challenge, especially the ones that hadn't gotten effects, we believe that food and media composites such as the acids and sugars affect this capacity of the media and whatever if you see the data, and also impact on scoop of food on the opinions of the components not understood. So we need to get our in-vitro assay, that may be in-vitro assays that it can put us to project this food effect changes in vivo and the doc model is a must. The other challengesto the facts is related […] to sabotage were the food effects are different and adults once you put a different type of needles andsequencing for the feeding and also that the virus concentrations in the pediatric subjects that are pretty much unknown at this time.So you're not sure how to get his information into a […]. PPI/ARA be a drag tracker predictively interactions that can be predicted mostly when it comes to PH, the degree of PH in the nationby specific PPI/ARA and if you take into account the timing of the

administration of the PPI in respect of the drug and the need is not fully understood the effect of these drugs on the stomach and thinking the effect stage, we know that they typically prolonged stomach emptying into the an incubationofstomach acid production, but they say we don't have really good idea what is the extentof this effect, and probably the more imaging studies here. The additional dosage shots that we know that many tracks nowadays are just an […] than the oral or IV drugs. So,subcutaneous and intra-muscular or committed ocular […] importance that we do, we have many, I would say great advancements in this understanding this route and creating of such models through this […], but still better definition of physiology of those inside this is needed. Also, differences in absorption from this escape side between different ethnicities are not well understood. And understanding the impact of recipients and is more science experiments in this area to perform a […] grip on that issue, and the major challenge is that it's hard to get this information and also there is lack of satisfactory amount of […] data for regulation purposes. When it comes to futuregoing back to the disease slide, we believe that thatmanaging PBPK models would be needed to be in better understanding of the disease and better protection of prediction of efficacy of the compounds in the future. So, here we have just a couple of case study models shown, but […] it would apply […] entire models of elements of them to be managed with PPK for better projection of the disease and probably the I'm opening that can can of worms about proprietary model platforms. And there have been lots of questions and I would like to say that when we look maybe the nature of platforms that are on the market, nowadays, it's been over 20 years of development in fairness traded quality control through rules, continuous software and code support and improvement that, I know we are called sometimes black boxes but some other set […] this is not a glass box you can actually see what's what's inside. You might not be allowed to touch certain end of the coat and you think I will detach myself you know? So Iuse this software formany many years because I'm not another program if you look at the software Wikimedia the class lines of code, it's a tall order to change that, right, because it can cause undecided differences and there are other […] manuals, publications and phone numbers to the company in the case you really want to know something good in the public domain. And sometimes I agree […], that we probably all know how to drive the car, but not necessarily making them ourselves from scratch, right? Or knowing every element, how these characters fields. And it's important for us that we, you know, know how to drive and it gets us from point A to point B. And that's where […]. Thank you very much.

Steve Hall: Thank you, Grace. Next, I'd like to invite PaulSeo to say a few words. I don't think Paul has slides to show, but I think that's fine. He's currently the Acting Director of the Division of Five Pharmaceutics in

the Office of New Drug Products, and oversees the direction and new processes for MBAs and abbreviated MBAs related to biopharmaceutic.

Paul Seo: Good afternoon, everyone.Before I begin, I wanted to thank the organizing committee that having having me on this panel. I've lot to say on the topic, but we've seeing it for lots of time. Hopefully some of it is new for you guys. I also want to thank Steve, for lending me the 5 minutes because it could go on for quite some time.I decided to live dangerously a little bit to not have slides this time, just like its speed off the cuff. And I'm going to change gears a little bit and talk about how we're using PBPK in the body ground.In doing that,I don't want to make assumptions. So let me explain. In your general drug development scheme, what we see, you have a clinician that has a clinical study and, for example, there's too many adverse events name one, formulators, Truncate Cmax. They go back to their formulators. It's not a really the only decision. They typically have some form of modeling and whether it's PBPK or something else, to help inform the decision of how the clinical study will be done at what levels and what in the formulation will look like.That being said,in the typical applications we get whether it's an MBA or an NPA, the PBPK model is quite robust. There are knowledge gaps from where I sit that I can go over. Some of the knowledge gaps there are twofold, one is logistical, one a scientific. The logistical gaps, I will say, are a little bit easier to overcome in some ways. Modeling is inherently technical, as many of you can attest. It's hard to really, from a regulatory perspective, hire unlimited monitors. There aren't many academic institutions and leaders in addition training our staff to be consistent and really be milers from that perspective is difficult. From my perspective, which is biopharmaceuticals, you have to have an understanding of manufacturing pharmaceutical sciences, in addition to the pharmacology aspects, and you can't really be a master either of those areas. But really, you're a generalist, so to speak. That being said, one of the examples I like to go over when it comes to the scientific gaps is everybody in this room is probably familiar with the Google Maps. If you map right now and take out your phone and you map out like, go from FDA to New York,it'll probably be several routes. Some will takeone half hours, depending on the traffic and other route might take you all the way the West Coast sense. San Francisco and then back to the east coast. So whatever Google uses in term in their logic we have a decision […] in the app, which do you choose?So that's one of the scientific gaps analogous to that as well as I see from my position. We might have the same set of data coming, but the modeling done by two different modelers mind, may end up in the same location in the same place and decision making, but how they got there will be inherently different. So, what's to say? Which one was correct? And that really goes back to the framework of the white paper on the walls while we're here to discuss. It just depends on your intent

of use and what the model is for. So in the Google Maps situation, maybe you might not get there as fast as you can, then Route A might be better. Maybe you want to see the Grand Canyon andall this other stuff before you get to your destination,then maybe that is the better route for you. So what I'm saying when it comes to modeling is your mileage may vary depending on what your company's a model for and the quality around what we've seen models used for our waivers in in vivo studies, formulation changes and that mostly deals in the supplement arena? One of the other gaps that I see when it comes to that speaking of formulation changes and a lot of other topics of the performing is, I think there's a lack of understanding of existing effects. We do understand what you're accepting and does at the end of the day, to an extent, in terms of the in vivo response, when I sent you a response, I mean PK, but from a mechanistic understanding, it's very limited, what we, what we really truly know. Are those stage need to be done? It's not on any one group agency or industry alone, I think we need to work together as a community to do that. The other piece, the other knowledge gap that I see from a quality perspective is a lack of understanding in terms of process and how you make the drug. Why does there's an example? There's a fine of you that know me the example I always use or analogy I always use is, if I have a batch of food ingredients, I give it to my 8-year-old, versus I give the same ingredients and give it to a chef, one will be a souffle, one will be a brown glob mass of something. So what that supposed to mean is process matters, how you make your drug matters. And understanding those parameters dictates how the absorption profile will look. In which case you now, if you know the observable parameter, and you know the clearance and how drug is eliminated, and you essentially know your PK partner in typical cases.So I think process of their effects into the study, and there's a gap there.There are several other gaps which I'm happy to go from the panel and I know I only have five minutes, I'm probably running short of time. In conclusion, I would like to say if we just fast forward 20 years in the future, when I look back at this time as an inflection point, really. WhereI think as a community, we've overcome the Delta G, so to speak, of our willingness to accept PBPK modeling when it comes to the scientific knowledge that we have and understanding the physiology, or the technological barriers that are there. I think we've come a long way, at least over the last 10 to 20 years from I've seen.So I think theuptake of an uptake and success of PBPK will depend greatly on all of us in the room. I know this is also the case, there is a general apprehension from the industry side to try something new, I will say, but at least from a regulatory perspective, not just MBAs and I can't speak on behalf of PMPA, AMA and whatnot, but the regulators have an intense desire to see new tools like PBK succeed. It not only helps reduce regulatory but increase its flexibility from our standpoint.And that being said,I think it's up to all of us to

close the gaps that exists, so I guess the same questions […]. Thank you.

Steve Hall: Thank you, Paul. Next is Marc Gastonguay. He's the founder and CEO of Metro Research Group, providing strategic financial modeling and simulations solutions.

Marc Gastonguay: Thank you, Steve, and thank you to the organizers for the invitation to participate today. The ideas in the […] just a brief few moments are those reflected by me and others mentorship from a particular method links, contributed tothe adjustments. So we think about knowledge gaps in the panelists here who had done nice job to identify the potential opportunities for growth, the areas that need further study, and I believe thatthat will continue to be the case that science evolves, right? The growth of science equates to a further understanding of the gaps in knowledge. So as we, as more informationemerges from quantitative physiology and pharmacology, as new therapeutic modalities and targets are entertained or model-based in modern form of decision making, they will contain the gaps.Those that they might call global knowledge gaps are also local knowledge gaps are where you need what you might call knowledge silos. And that's what happens in case when knowledge is constrained within a particular tool or subset of community. You know, an example of that is that currently, most of the published PBPK model results are not reproducible with independent pieces of software in these opportunities with respect to sharing through competitive learnings. So the concept that I'd like to focus, is focus on is an open science driven concept to bridging knowledge gaps. Five different theme chapters hit on these quickly, and hopefully we can discuss in more detail later. The first is disentangling the model from the software. PBPK models should be able to be specified completely independently from a piece of software that requires transparent or difficult loss justification. And also an open provenance on model parameters and their derivations.Coupled with that, we need a separate quality software development, life cycles, and model development cycles. And I also advocate for community engagement and verification validation models.The first time disentangling software from models. We mentioned this earlier today in the discussion sessions, you know that the goals are not always aligned between the science and software development, and there certainly arecommercial incentives and important needs to be served by like commercial software. However, tangling the science within the software is not the best thing for the community and that it doesn't allow for the independent evaluation […]. Reproducibility of models and transparent mom specification, you know, the National Research Council in their 2012 Paper Con Verification Validation and certainly quantification highlighted the most important mechanism for ensuring credibility models is an open and transparent presentation of that model.We can answer that again for that respective structural model transparency. Also, the statistical model of transparency is going to be thinking now about bridging the

structural understanding of mechanism to intercept the variability or hierarchy of the uncertainty parameter estimates. This can also be specified in the transparent way. And you might consider specific software implementation transparency, but not something that locks a particular model to one […]. With respect to the provenance of the model parameter derivation, the data inputs that it models, it would be in the future ideal for each parameter to be defined with source species unit sample size, precision disease states, and all of this may be captured into some sort of a standard format, to something that could be […] format that allows specification of these each of these components. It also would allow for transparent exploration of alternative parameters sources and looking at sensitivity. One of the questions that we haven't addressed today iswhen we can't validate the model, where we don't have data to assess the performance of the model? To what extent do the deficiencies or uncertainties in the model lead us straight and effectiveness, decision making.And open and transparent acknowledgement of those uncertainties will go a long way to that name.You know, the software development lifecycle professional software developers know how to do this very well. Where requirements and tests, implementation acceptance criteria, documentation, that's all part of the process. The same thing can be done in an open framework for model development.Imagine the improvement example we heard about earlier today where the software was changing over time. What if that was done in an open model development lifecycle where community contributors could challenge and even see the updates in the model along the way, and adjusted decisions and use of the software? Finally, community engagement and verificationvalidation of the model of software. You know, this will undoubtedly improve quality.The famous statement by Raymond with respect to open source software given enough eyeballs on lots of challenges, the same concept applies here with open model.It also allows for scientific relevance, very scientific expertise to impact the development of the model. And of course, widespread documented and qualified testing least credibility and understanding, the more broadly that's understood the more credible models. So, thanks for your attention and I look forward to the discussion.

Steve Hall: Thank you, Marc, and the final panelist, who's come to take a couple of minutes is not to take it on paper. Anyway, he’s the director at Novartis who leads global PBPK model […] PBPK scientists and services […] and biopharmaceutics experts. […] I can't say he can, PBPK today […].

Tycho Heimbach: […] PBPK and Mac. Yes, so I am the last speaker, it's difficult to cover something new here after the so many exciting topics […]. Yeah, I think the other speakers already talked a lot today about what can be predicted is confidence by conventional reversible nonprofit complex DDI studies etc. And he, what I decided to do since […] involved with

most pediatric predictions as well as organ in […] two cases of examples where we are trying to use the PBPK clinical class. Supplementing means that we will have some limited PBPK data. We're trying to predict the variability in the population. And this comes back to what I think Don Mager talked about a very early in today about having modeling films directly relevant to what more efficiencyoriginally this case example of a sneak out in the tacit knowledge is the kinase inhibitor was inspired by regulatory request, wherever you are questioned about the body surface area doses that we had posed in different age groups in children and you can see here that our original proposal the day I read a function of you know, the age of six was senior is not sufficient, and we were asked, the sponsor was asked to provide additional justification on the body surface area dosing and to generate a more valid modeling approach to the age group of 6. You can read the details in the publication that came out in February. But you can see here that we have course they want data and we have steady state data, loading up Stephen chronically. And you can see that we have used model verification with adults not showing here, but 12 to 18 years old, 6 to 12 year olds, 2 to 6 year old. I would like to point your attention tothe lower panel on the left to the 2 to 6 year olds, we have only one profile one child. There's no other children and we have had steady state to other children, where we collected some data. We use the PBPK model to describe this data and not only very able to justify the […] it's okay to go to those. So to answer the milligram per square meter can be used for all age groups. We also have a label extension only documents based on this very limited PK data, and the second example of very trying to better use PBPK modeling to supplement the trials is in the space of a hepatic impairment that we heard a lot about today, where I think Steve and Yaning have mentioned that we are not quite there yet with the predictions in the severe impairment. So we have a Compound Z, where we have rapid absorption distribution is governed by very high plasma protein binding. Metabolism is nonCYP-mediated and there's no renewal clearance. But the question that we were trying to answer is can the PBPK model predict and supplement the limited clinical PK data that we have, which is the end of two we have two patients, two patients to 10 years to recruit. So the current requirement is to minors, six patients. We can calculate out if we can extrapolate how long it's going to take to record another for patients. And I don't want to go into the detail here, but we had a model strategy, which model the data and control subjects will be measured as it meant concentration, you heard already earlier that avenues to be reduced in the presence of hepatic impairment, and this compound is added to the ground. And be measured it […] into patients and be set up a model not just for the Compound z but also for everyone.And here's some of the data that's this is a very important slide I think. You can see in the upper left, this is the control,control

population N=10 and then you can see the mild impairment N=6. We're trying to describe the variability as you can see that the variability is overall well described all there was one patient, which has higher Cmax concentrations and then in the lower panel you can see we have the moderate argument with an N=4 and then disappear apparent reason N=2 which were a wall captured with the moral. So the question is under which conditions PBPK modeling can be leading to increase the efficiency in the drug development process such that perhaps you could run a study with me before in the moderate impairment or N=6 in the severe impairment, and basically we described the model using multiple study data. We included the algorithmic concentration, which are not shown here. And we believe that this is one of this unmet needs where we probably need more community data, we need to look at individual data. You know that in the IQ consortium being described earlier you know, if you haven't geometric me data don't have individual data, I would submit to the FDA higher 10 or 20 […], look at all the individual data and see what we can do with it, and I'm going to close out of here for the discussion, but in any event, we showed that the compound here had more severe, reduced AUC because of the rest of model and more free document was available because everyone concentration was reduced is all predicted values and a close here maybe we can have some discussion. Thank you.

Steve Hall: Thank you, Tycho. I think what we'd like to do now is open up for discussion. Please […] discussion points that you feel were raised by the panelists or just questions that you think they may be able to […].We have, I think three fourths of an hour. Soplease,maybe maybe we can we can get started with. Let's go back to Marc. I mean, I think maybethere was some shivers running down the spine of some people thought of using open source of software to submit their regulatory documents to the FDA.I mean, can you see that really working in reality?

Marc Gastonguay: So first of all, what I said was open science open models that doesn't necessarily require open source software and that was the distinction that everyone made specifically between specify models can be sent into software. Ideally, an open model to be specified in commercial piece of software for an open source piece of software or general purpose pieces software. It doesn't really matter? That was the first one. But secondarily, we submitanalyses all the time in terms of ourotherregulatory agencies. Open Source does not mean, is not synonymous with a lack of quality. Any software can be high quality, and reliable, validated as well. I thinkthe real emphasis there is that the users of that software, both the scientists and the […], and regulators need to make that own their own evaluation about that.Let's

not equate open source with poor quality more commercial with […], so let's not make such a simplification.

Steve Hall: Can you can you speak to the challenges in sort of thevalidation world where perhaps these models could be changing on a fairly frequent basis as the community finds, you know, ways to update them?

Marc Gastonguay: Yeah, absolutely. I think there's a, there's a nice example for this in the open source world, and it has to do with the physical side of things, our packages, where there's a lot of changes and backup versions, but we still through delivery methods can manage those versions, we can make that a reproducible analysis. And we canlink having accountability trail from a particular analysis version of the software, same thing can be done for a model […]. We have version control […] to do this. It's done in software development […].

Steve Hall: So Iain or Grace, do you have any comments? How do you seethe world, which we would use perhaps a combination of the glass box and the opportunity […] environment?

Iain Gardner: So, I would say that,at least for from a […] perspective, we always try to believe in open science and actually put in the models in their name and the way that we work with the consultant image through and process and that's why,for instance, that the analysis the young show before originally, there was nothing to the model when we started in DDI simulations in 1999, it didn't work straight away. There was a lot ofeffort from scientists with incentive and also,you know, within the pharmaceutical industry to develop models and make sure that […] if things are working properly so from that side, we're completely fine with with open science and sharing models. We we've always been […]

Grace Fraczkiewicz: […] conscious of you have to look so it depends what does it mean open science and software, right because yes, we can show the science. We might not show or learn technological solutions, right because let's face the truth and as a commercial company we spend millions and millions of dollars on to implement certain solutions that work and it doesn't come cheap right so we not necessarily want to disclose all the solutions. We are open sharing which you can see what is the model structure? What are the maybe physiological components andmost of the equations, we don't start out words and some information that, you know that because it has to be proprietary in order for a company to in return that investment.

Steve Hall: So behind, I don't know maybe, Paul, in your part of the world you have some experience with these issues?

Paul Seo: We do, so […] models all different ways, both with our and […] software.There are pros and cons of going either direction.One of the

pros of using open source software is when the regulators have a question. Company sponsors quickly adapt and implemented into their model. When there a lack, when we have a question due tomaybe something not being addressed in the model, and they're using commercially available software. Generally, the goal around has been to do it outside of the software and excel, and you certainly implement that […]. In either regard it works, but there's a learning curve for the regulators and the […]. So just echoing what Marc was saying, I think there is value in going with open source.So we don't have an opinion in terms of which software or open source to use but they're all […].

Steve Hall: Any audience thoughts as to what that will look like if you were using something in addition, instead of CMC […]?

Audience Member 14: This is Nicholas Pfizer […] it comes down to more of an open science aspect. I also wondered how industry elements can and one other consortium provided data and provided clinical information, but it seems to be a case where all data is necessary. Some validation, sensory analysis […] qualification, as it appears indecisive. How can we support this concept?

Paul Seo: I'll take a stab at that.So one of the […] gaps that I went overnot everyone is naturally modeler that's not their background. So when we get a file and package it, I would say the best smiling package that we received today at least for my assessors and reviewers is one that explains that follows the framework that we have outlined in that white paper. It explains the purpose of the model. And then they walk you through step by step, why they did certain things, some, some aspects of the model, besides being technical, you really have to be conditioned to really appreciate the grasp of what you're trying to do. Whether it's something that, for example, […] product, there was something that we missed, but the clinician had indicated. So when you look at our information, so we were able to adjust the model with respect to Clarence, and, and main, the mouth is all of a sudden work better. So when you're submitting the model, in addition to them having a very clean modeling report, I would say, step by step explanation of why you're doing certain things in case of explaining it included screenshots of what they did and how they did it. It was very helpful. I use that as a key example.

Marc Gastonguay: With respect to the industry inputs in an open science, I think, sharing knowledge, pre-competitive knowledge that's appropriate. And also vetting the tools that are that are available and publiclysharing results of your own exploration […]. You know in the end, it's up to the stakeholders to decide what was the best way with the government, and I want to acknowledge excellent science has been done by the commercial vendors here.When we think about the new problems that we have to tackle the future, how rapidly do we want to tackle or

approach those as […] knowledge bases or as aunified community moving forward to build that knowledge and quantitative way whether or not that's done in commercial software is a separate question, but the models themselves certainly have, tend to benefit more rapidly gaining credibility becoming more accurate when they're exposed to a larger audience.

Steve Hall: We have a question or comment at the back. Could you state your name and your affiliation, please?

Yuching Yang: This is Eugenia from the Office of Clinical Pharmacology EPN and, so,so first of all I want to emphasize, to touch in a very light and I would say gentle way. So basically, the effort and the knowledge to invest into how to pick, select, analyze, curate […] concept to support support any model, as it is difficult. All I'm trying to trying to express here is when we're looking atsoftware, open source open science, a lot of time we are really looking at the peace of mind or quality, how you use your data, part of your thinking process or the use of accumulation of the knowledge over over the whole science not onlyfrom college, maybe all the way back to the end of this morning talking about the CFD model. So, the problem is, I will not say a problem, certainly from a FDA's perspective, we want open science, because open science is not only all academic is also from reviewer for any company they know and that they know how to choose is basically that is critical, but that the other thing is once we have open source then we, the label of the investment in terms of verified each cast away, each parameter, left hand of investment from the review upon the view lab is a great burden. It does not mean we are not looking forward at the post point with the open source, you can quickly adapt the model feature and if I want to move to more interaction that isthe major talking about interaction with other type of modeling, that is one morefeasible way to go. But I also want to point out lack of the quality of PPK analysis or any type of mechanism […] analysis beside the code, beside the equation. That is the quality of the data or the quality of the model. Thank you.

Steve Hall: Thank you.

Nina Isoherranen: Nina Isoherranen from the University of Washington. I just want to bring in academic view for the open source discussion. Because I think one of the issues is that a lot of real life cases are more complex than what a software allows you to do. So for example, when you have three or four parallel, and otherwise, if one of them happens to be active or inhibitory or whatever, I don't know or settle software package now that would allow me to model that kind of complex scenario. The same goes for, for example, in four corners of themixture of force, there is mercy again, and I want to create a substance. I don't know that you can actually model for those at the same time with current close source

software. So I think there is a real need to actually encourage people to not only train future scientists in open source modeling platforms to teach them how to develop models for something that we don't have models for yet. So I just wanted to put that out there thatnot all the PBPK problems can be solved by the current closers.

Steve Hall: Thank you. I think, those those are very good points, and if think if you guys at the University of Washington can committed to training your people, basically I think you'd be doing all of us a big favor.

Nina Isoherranen: So as you know, as former academic, we have to support our graduate students, so anybody who wants to support training of graduate students, I will happily take as many trainees as part […] support.

Issam Zineh: With all the discussion, I'm Issam Zineh. I'm interested in the question of Marc raised this issue of communicating with your experienced platforms, sort of one piece of it and the second is just how good is the model? And I'm concerned about publication bias. And I don't know if this is a sort of a reasonableconcern in the modern era, maybe the field is already happening, I don't know. But to get into peer review, you only have to have shown you did pretty well with your model predictions. And so there's, we have no idea what the denominator isin terms of the modeling space, so can if you comment a little bit on sort of what's the current state with respect to kind of, you know, either cross platform comparison, that's one issue and then the issue of is their space in the biomedical literature for describing less thanstellar results with modeling solutions.

Marc Gastonguay: it was a great questions. I think, with respect to comparability across platforms speaks specifically to that, […] cases and you know, the challenges that any literature publication, even for simple models of population, […], there's typically insufficient data to exactly […] except for one, and then even the model specification themselves are short.Maybe somebody skilled in the art do come pretty close, but the executivevery difficult. So one of the suggestions and some societies, this is they actually have an open source repositories where the model is available in some code. It's non-commercial or easily accessible […] repository, where that's available people to pull that down, compare that code is simulations with that codethat's published in the paper. That's also a place where the community can record these open source repositories of open source software can also be applied to open models. And that's the framework where issues can be raised. Here's a different result or a different parameters or source for that, right?It fosters community engagement and transparency that eventually leads to […].

Iain Gardner: SoI guess there's a few things first and foremost, I'm Iain Gardner, head scientist […] clarification for that. But I think the models and parameters can be available and are available in literature. All the information are there. It becomes more difficult to put the source […] it's 2 million lines of source code and it's ourcandidates been developed over the years. I'm not quite sure how we would make that available. So you know, there are things we can do so the models can be transformative into other languages I guess, but then you're still not comparing exactly the same thing. So that's something that we need to work out as a community the best way to do but certainly the models and all of the parameters and the boundaries thatthe public domain […]. Okay, thanks.

Audience Member 15: All the speakers kind of nicely identify gasps, potential solutions, but I didn't hear sort of the next steps is that they can dissolve in terms of their validating the system parameters with the software developers, or is there going to be a guideline? Or is it an IQ work group that's going to take this off? Maybe the panel can share their thoughts perhaps this could bejust today?

Tycho Heimbach: Yeah, I think you because […] you mentioned I do consulting, right. So I also do, of course, […] big pharma companies are part of that indicated, you usually don't share the individual patient data. And I still wonder if, perhaps when you're talking about further improving the models, we would be to advise or at least the agency to look at the patient data can be described as a very different, two different populations. To me in the IQ that has been cloud since I've been accomplished, you know, you mentioned earlierthere is of course, the virus for coming out today, for example, that fuse for see predictions were not particularly […] needs to be further improved. But I think, you know, it's a very competitive space, we're doing quite well. But again, because we don't do the share the individual data, maybe do something at the FDA, because we must have all the data for all the studies, for example, with all the individual subjects.

Iain Gardner: Just a common philosophy, you know, you should take swing in your flat. Since you're […], so you look at the OpenStack and projects, which puts a lot of companies and academic constituents working together to try and look at ways to create real absorption prediction. And so that was a completely European from the project, you know the results from that. […] available. So there are done and we are happy to cover. […] initiative […] in the end like making models better and more suited to answer the questions that we need him to answer as well. Everybody wants to know those kind of collaborative efforts. […].

Paul Seo: So, to basic answer that question is no, we don't have plans. We are in a particular situation, where can we get an application and there's no getting in there. […] particular if we have a luxury of running that

information across the lifecycle of that product, whether it's from inception all the way if we have it for Han VA, or supplement or whatnot. And a lot of times, especially one reviewer is one, they'll run across different programs and kind of verifies validates in some way. I do love the idea of having a code repository like Github. When you do that, essentially, what you end up doing is standardizing the model. You have a certain measure of self-policing by the industry, which I think is highly useful.So I'm not saying that will happen in the FDA, but at least in the future, the nice to see something like that.

Audience Member: Jinjin from Genentech, I havetwo related comments more specifically given the complexity as the “PBPK,” which I think are unique challenge we have. One comments about the open science, I agree many of the things are published interrogate the model structure. It like that, however, is open science opening enough to enable is reproducible cells. I think that the different question because these models are very complex, especially have a lot of combat interceptor are broken it into correlation of those interceptor abilities, many of those, I always say in the details. In PBPK type of model, many of these detailed level of information are not necessarily 40 publish, therefore, it's very hard to transfer these open size to reproducible science via given scientists. I think that's one comment. The other comment is more about the open source software. I think there another challenge probably with this type of complex model is, is tailored it depends on the different users. In the user for me as a hands on modeler, I love the idea of having the code therefore, I can customize model especially today to PD component is key component that will keep the hands on modeler a lot flexibility. However, I do see also the challenge of these type of open source is such a complex model, it can be counterproductive from our user groups. For example, imagine the open source code that you need to understand the code, why my life to be fully utilized model even […]. So, then it will limit the user to the ones that are really very knowledgeable of the entire code rather than some of these commercial software's where if you focus more on the so basically I like the glass box analogy. So basically, you can see you can understand what's going there but you don't need to worry about on your touch the model, you messed up some of the individual relations […] glass box. So I think, I don't have a solution. But I do see that this type of very complex models, the open sourceconcept does provide some of these new challenges for the different user talking about […].

Tycho Heimbach: Thank you. Can I make a comment because I will submit that at least a lot of the PBPK model information is already expanded NDA or typically is […] formulation information, and certain, certain things around here so really the […] if I know the, what's available on why this works, the lot of information is really publicly available. So if you are

practicing, I'm thinking you cannot do it in one or two hours. We will have to digitally scan the data reports out there and you should be able to reproduce the […]. My understanding at least the Office of Clinical Pharmacology has been analyzing data that was submitted by companies, including my own to duplicate our model is appropriate. In some cases, same changes were suggested.

Steve Hall: So maybe maybe we could move on to a new topic. You know, much of the discussion was about things that may or may not happen in the future and almost without fail, we came back to the knowledge gaps that sort of prevent us moving forward with the […] formulation of issues. How do how do we fill these knowledge gaps is a very challenging situation. Many of the folks involved in the[…], this can be in a position to generate large amounts of data that could be particularly political data that that could serve that purpose. So, with how do we move forward in filling some of these, these gaps that we have?

Iain Gardner: I think, as always, it comes on to collaboration. I mean, going back to theimpairment, one of the problems with trying to make accurate […] the clinical classification we used is quite broad. In our champion, the champion sinkers lots of individuals, and there are many other classification systems as a community to evaluate to see whether we can produce models using other classification systems that would allow us to move forward more accurately. Triple A is […] that there isn't a lot of dataavailable by the patients.So, they can see other classification systems like that, which is a very, very broad […] that's one of the reasons why […] affects everybody. So the what is damaged […] a resolution of that, […].

Steve Hall: Thank you.

Tycho Heimbach: For clarification, so if data is submitted […] very easy to find, but sometimes these false marketing commitment for information request at least to my knowledge, they can be difficult to find the words they're […] posting. I do not know the regulatory framework for these, but for example if you're talking about a special property data that will then analyzed by some software as part of regular reply than post NDA. These ata or could these data be this also posted by the NDA is? Is this a question for the right person?

Xinyuan Zhang: […] I think in general, […] information act on the journey to end the interviews are published and road to the […] reviews for […] reviews are generally published. Again, talking about the Open Science, I think all these models […], all this drug practice and information studies, they are going to the sponsors are […], we don't want anything. So as I can tell you the community as a whole, […]

advance, it's really depends on the applicant or sponsors or how you want to […] this, that they acknowledge specific drugs or specific […].

Tycho Heimbach: Thank you for the clarification. I, I'd like to think at least part of theclinical trial of communication that the data, will offer the share from from the industry. Again, formulation, specific patent related information that probably cannot be shared for competitive reasons. Butif you are looking at studies that we published, my personal opinion is I have a hard time imagining why like real life kind of environments that these specific profiles would be published more and more routinely and easy to find. I every time, I know some of these data is hard to find sometimes.

Grace Fraczkiewicz: From my experience with dealing with customers, it's sometimes very often very difficult to convincethe customer who wants to live application to show individual data, which let's face the truth, that the image data are very often not representative of the individual by the subject of the data, if you look at his clothes, and there is richness of information just in this individual data, so having the model but then on the other take typical sector, sometimes judgmental, but if you have enough experience, […] them and then extracted, extracting the physiological and whatever population components that affect absorption from this individual data it provides, the richness of information, but we are not allowed to publish it even if we build them out for specific company, we are not allowed to pass individual data and I sometimes don't understand why is this field, why is […].

Paul Seo: Do you think that your data is a protected data to an extent it's considered IP? So when you do an official request, you won't see individual data you'll see me there.I know this because when we try to use a model across applications across a product line, we're not able to do so companies that we're trying to bridge are, kind of look at that. They don't have product reference to each other. So we have the same difficulties, when […], I guess. I'm not sure that there's a way to go around.

Steve Hall: So I think as we move forward in the PBPK world becomes increasingly complex as we move into new areas and new opportunities, realized that something Paul said that made me really wonder whether the review process is able to keep up with that complexity and volume of work that that would be coming, coming your way. So I wonder if you have any, any thoughts about that? What is the solution? Is there, is there a real problem? And if there a solution to having more reviewers, more communication, more interaction with the customer base that would allow models to be vetted perhaps earlier? Is that something that's that's doable to just not?

Paul Seo: I think it is doable. I unfortunately don't have the answer.I will say right now I'm in the worst or best case scenario, you have to imagine if this kind of model was submitted with every application. What do we do as an agency?Right now, I would say, all we have is the brute force method, which is one at a time. And then, there are certainly other things that agency can do. I think, technically, you're speaking with having some kind of committee of sorts that goes cross center, whatnot. We do have one in my division.I see some of them in the audience. I think someone would put them on the spot, but committees certainly helpoversee what comes in and what comes out and provide some granularity and consistency and training even, but I'm not sure unless we start looking at ways to really automate this process. What that would look like to help ease the regulatory burden.

Steve Hall: A weeks ago the IZ were at ease and sort of alluding to the fact that maybe the MIDD program could be expanded and perhaps that could provide a path to greater discussion and communication. That's something you'd like to talk about?

Xinyuan Zhang: […] talk at a time from my reviewers […]. So you were mentioning and reviewers. I don't think any reviewers is the complete solution. As you can see some of the issues need to be resolved outside of the program on review samples. While some of the issues can be resolved, […], so we first have to differentiate those, which issues to be resolved outside and which needed to be resolved outside and which issues can be resolved with me as I've added. Keep adding reviews won't essentially resolve the questions. Of course, having more reviews is always empty. We can have more time to do research to look at the data and move on and those type of things.

Issam Zineh: […]. So in terms of the MIDD experience, the MIDD pilot program, to those familiar, it's a dedicated sort of regulatory avenues to deal with these issues to be studied. And just a couple of things. I mean, I think the pressures really on my regular, regulators, I've seen these models for the first time and an NDA or the VLA. You know, you have10 months if you're lucky to get comfortable with all of this, but it's usually in especially in areas as I medical lead, where these models probably have their biggest return on investment. Much more […] of timelines. And so I think less shifting that interaction could be very helpful. And so we've had a number of this MIDD experience to much more direct engagement is the subject matter expertise and within the FDA, and counterparts in companies to address these issues. A couple of important things. One is those conversations are made very conceptual. So it offers the key there is to get alignment on what is the modeling strategy, what's the intended use? Are we trying to use this model to do from a drug development and regulatory clinical perspective? So any clarity on that early on? And then what are

what's the sort of extra, what are the exercises that needs to be done in order to […] to that approach, very helpful because then when you do see these coming later development, it's not the first time that we're looking at it. It also allows for the opportunity for the multidisciplinary team to get comfortable with this. Again, remember, this is not a model to model question. There was a point made earlier about what we're already doing this in response to adventure framework that says modeling. That's a mother's mindset. It's not a mindset, we need some sort of conceptual framework to have discussions around risk and around with decisions we're trying to perform and so the MIDD program allows all of the key decision makers be respective of where they call out whether it's clinical pharmacology, quantitative, statistics, medical, chemistry, etc.to be at the table of discussions. We are still sort of, there still a school of thought that we still need that deep dive on the model even at that stage, but I can tell you, that's not everyone's perspective, but it is important perspective. And so if we do expand this program now, to have more bandwidth, to deal with these issues in ID space, we still need to resolve that question about what's the level of intensity of effort that's required in terms of regulatory evaluation. So whether it's an evidentiary framework or a risk based approach that was presented earlier, whether it's some sort of, you know, guidance to the community on how to come in to regulatory bodies, with the sort of the most parsimonious performances package, I think we'll need to sort of be more experienced on what's the biggest,what's going to be the biggest claim on it.

Steve Hall: Thank you very much.So I see we have about five minutes. If any members of the audience have something perhaps not, not something we've already touched on some some ideas, some thoughts about where we're going and what we need […], this would be the good time for you to bring it out into the open. No? No further questions? Anything further from the panel. We're done. Thank you very much. […]

Lauren Milligan: Thank you everyone. I'm going to now Dr. […] backup for some concluding remarks.

IssamZineh: Okay, thanks Lauren. I will be very brief. This has been really an exceptionalday. So I'll try to, I know I won't do justice to all the nuances of the discussion, but I'll do my best to summarize in a high level and then with maybe some thoughts to one next up is acknowledgement. So today we heard early on from leadership in both CDER and CBER about the trends in small molecule biologics development and highlighted the potential and the actual role of MIDD PBPK included in increasing efficiency and enhancing regulatory evaluation in the first session we have three really excellent speakers who highlighted a range of high level scientific and regulatory issues in the application of PBPK, across the continuum of drug discovery, drug development and regulatory evaluation. And in our second session, we propose the risk based framework for PBPK model assessment. This was followed by really robust discussions. And I think it's worth pointing out a couple of key points that were at least issues that were explored. These included why we chose PBPK as the sort of test case for this framework. We talked about similarities between the concepts of this framework and existing guidelines and current practices and what might be the value add of such a framework in large There was actual discussion around the framework as a communication framework to enable discussions at an early stage. In in addition, we talked about the need for balancing model a high level evidentiary framework with maybe morespecific decisioncriteria for what we're being referred to as credibility goals and the need for balancing transparency and directedness with being careful not to be too rigid with any one particular potentially construct. We also talked a bit about considerations around harmonization. And we really talked about questions on how to practically apply such an evidentiary framework and there was what I heard was there was a call for a need for additionalillustrative test cases and we welcome them. We also discuss the importance of continued research to elucidate some of the biology and mechanism that's informing PBPK. There was discussion around how to deal with the issue of dynamism and modeling and simulation. And we do have some analogies from care to software as a medical device experience as well as their digital health program. And of course, the question at the end, which was really important and carried over into the later in the day was the delineation between the software and the modeling as well. Italso, we, in the third session, had very illuminating talks and discussion around practical application of PBPK in drug development and our recent review experience. This was really important in terms of highlighting the scientific considerations and complexities and good practices that are needed for responsible application in a fit for purpose way, and of course in the final session we had really important discussion around the future of

PBPK that were really interesting sort of futuristic thoughts about expandingthe application spaceto include precision dosing in therapeutic individualization as well as some of the other regulatory and drug development applications that we know well. In the barriers and opportunities for alignment discussion. In no particular order. We heard about lack of publicly available data, a lot of discussion around open source, some scientific and technicalneeds, including but not limited to, lack of IV data and response variability data in certain contexts as well as need for better mutual assets and other situations. We talked about the issues around with review or evaluation on sort of the proprietary modeling platforms. It was raised that one of the barriersis really a subject matter expertise, bandwidth within the regulatory environment as well. Also emerging, constantly emerging biological insights, as well as novel therapeutic modalities are also raising challenges in terms of being able to, in real time, incorporate some of the contemporary science into the decision making. We heard about interesting five factor, five element framework for still facilitation of open science and you got into crowdsourcing. And finally, we ended with some discussion around consideration for review models and how this gets implemented in the FDA and other regulatory capacities, situations in context and environments. So I want to talk a little about next steps. Suffice it to say there's a lot here. And in anticipation that this was going to be a really dynamic workshop. We are set for a debrief within the FDA that really spans across multiple functional units within multiple centers. I think this workshop clearly demonstrates the need for an action plan around further dialogue and the evidentiary space as well as some of the regulatory science discussions. So we expect further dialogue internally, we hope for reactions input and more experience sharing, driven by outside scientists. In terms of open questions. I'm sure many of you have your own open questions I listed down just a few. And that is a fundamental question of is it even possible to have an overarching evidentiary framework in modeling for drug development and if so good, be brought to bear for PBPK. If not, this framework, what framework or what variations on the might there be that might make this reality?What would be the barriers toimplementation? It's an open question. And I heard issues that range from what I would call cultural issues to operational issues as well as some scientific issues. And the question is, is inherently non translatable? Are there some insights that can be gleaned from the proposal that would drive future discussions and future future iterations and implementation of what's the best mechanism for information sharing both in terms of just a general PBPK experience in drug development, and in research, as well as for those who choose to use this framework and kind of pressure test it. What's the best way to share that experience both within the community at large as well as with regulatory agencies. And what's next from the standpoint of policy

development. And we hope that many of you in the audience will be thought partners in this exercise and look forward to that, to that engagement. I want to end on another big acknowledgement. So I, almost every, every speaker and moderator really was very appreciative of the planning committee here. I just want to emphasize that this, this planning has gone on for 11 months for this workshop. And it was sort of all hands on deck to make this workshop. The success and it was unbelievable. It met, it even exceeded expectations. If anyone was on the committee or 16 people that was on we're on this community, raise your hands if you're still here. I ask you to stand up and take a bow, and if you look around, you may see some familiar faces. But these individuals came from the Office of Clinical Pharmacology, the Office of Generic Drugs, the Office of Pharmaceutical Quality and CBER and it was really critical to have that input. Thank you very much, the moderators and […] gratitude to the moderators, […], Dr. Hall and Dr. Wang, not only did they do a masterful job today, but really did a lot of legwork behind the scenes in terms of shaping content and working with the presenters and the and the panelists. I also want to acknowledge Kim Bergman and our labeling and health communication team that really raise the visibility around this opportunity. […] record two in term of attendance. I want to acknowledge the executive program or project management staff in the Office of Clinical Pharmacology as well. I'm hoping I'm not missing anybody. I do want to acknowledge of just maybe a couple more people. […] and her team and CPT PSP, were really helpful in ensuring a rigorous peer review of this paper that you're seeing here and working with us to make sure that this was out in a timely way. And whoever you were the peer reviewers, I think you either might be in the room or on the line. Thank you very much for your thoughtful comments. There's a lot of passion behind peer review. I also want to acknowledge all the folks that are listed here as authors on this publication. This was not easy actually, if you think harmonizing this was a microcosm of how challenging it will be to harmonizeany evidentiary standard on, upon modeling for drug development and we were starting with a precedent here. So this was the part of work and all the folks that are acknowledged here are mostly […] are listed here that provided critical feedback in the construct of manuscript. Thank you very much for your work over the past several months. And finally, of course of thanking you, the attendees. I believe that the discussion was really critical for us to hear from the crowd in terms of on the FDA side. And we're really looking at one of extend an invitation. We see this is the beginning of the dialogue and so we look forward to any input after this workshop. And look forward to receiving that and continue a conversation about how do you advanced modeling for drug development PBPK for the benefit of patients and drug involvement, and with that, we […]. Thank you very much.