FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY ADVISORY COMMITTEE MEETING

(PSCP)

Tuesday, May 7, 2019

8:59 a.m. to 3:19 p.m.

FDA White Oak Campus

Building 31 Conference Center

The Great Room

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Jay R. Fajiculay, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY ADVISORY COMMITTEE MEMBERS (Voting)

Paul M. Beringer, PharmD

Professor of Clinical Pharmacy

University of Southern California, School of Pharmacy

Los Angeles, California

Jeffery M. Carrico, PharmD, BCPS

Service Chief

Clinical Pharmacy and Investigational Drug Research

Member, Institutional Review Board (IRB)

National Institutes of Health (NIH), Clinical Center

Bethesda, Maryland

Jerry M. Collins, PhD
Associate Director for Developmental Therapeutics
Division of Cancer Treatment and Diagnosis
National Cancer Institute, NIH
Rockville, Maryland

Maureen D. Donovan, PhD
Associate Dean for Undergraduate Education
University of Iowa, College of Pharmacy
Iowa City, Iowa

Sandra Finestone, PsyD
(Consumer Representative)
Executive Director
Association of Cancer Patient Educators
Irvine, California

Tonglei Li, PhD
Allen Chao Chair and Professor
Department of Industrial & Physical Pharmacy
Purdue University, College of Pharmacy
West Lafayette, Indiana

Walter K. Kraft, MD, MS, FACP
Professor of Pharmacology, Medicine & Surgery
Department of Pharmacology and Experimental Therapeutics
Thomas Jefferson University
Philadelphia, Pennsylvania

Kenneth R. Morris, PhD
Director and Professor
Lachman Institute for Pharmaceutical Analysis
Long Island University Brooklyn Campus
Arnold & Marie Schwartz College of Pharmacy and Health Sciences
Brooklyn, New York

Eric Slud, PhD
Area Chief for Mathematical Statistics
Center for Statistical Research and Methodology
U.S. Census Bureau
Professor, Statistics Program, Mathematics Dept.
University of Maryland College Park
College Park, Maryland

Duxin Sun, PhD

J.G. Searle Endowed Professor of Pharmaceutical Sciences

Director, Pharmacokinetics Core

The University of Michigan, College of Pharmacy

Ann Arbor, Michigan

Andre Terzic, MD, PhD, FAHA

(Chairperson)

Professor of Medicine and Pharmacology

Center For Regenerative Medicine

Mayo Clinic

Rochester, Minnesota

PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY ADVISORY COMMITTEE MEMBERS (Non-Voting)

Walid M. Awni, PhD

(Industry Representative)

Former Vice President, Clinical Pharmacology and Pharmacometrics

AbbVie

Awni Biopharmaceutical Consulting, LLC

Riverwoods, Illinois

Jack A. Cook, PhD

(Industry Representative)

Vice President, Clinical Pharmacology

Global Product Development

Pfizer, Inc.

Groton, Connecticut

Srini Tenjarla, PhD

(Industry Representative)

Vice President and Head of Global Pharmaceutical Sciences

Shire

Lexington, Massachusetts

TEMPORARY MEMBERS (Voting)

Thomas C. Dowling, PharmD, PhD

Professor and Assistant Dean of Research and Development

Director, Office of Research and Sponsored Programs

Ferris State University, College of Pharmacy

Grand Rapids, Michigan

Patrick H. Nachman, MD
Professor of Medicine
Director, Division of Renal Diseases and Hypertension
Director, Minnesota Multidisciplinary Vasculitis Program
University of Minnesota
Minneapolis, Minnesota

Thomas D. Nolin, PharmD, PhD
Associate Professor of Pharmacy and Therapeutics
Center for Clinical Pharmaceutical Sciences
Department of Pharmacy and Therapeutics
University of Pittsburgh School of Pharmacy
Pittsburgh, Pennsylvania

Manjunath (Amit) P. Pai, PharmD, FCP
Associate Professor of Clinical Pharmacy
College of Pharmacy
University of Michigan
Ann Arbor, Michigan

Patricia W. Slattum, PharmD, PhD, BGCP
Professor of Pharmacotherapy and Outcomes Science
(retired)
Virginia Commonwealth University
Richmond, Virginia

Ravi Thadhani, MD, MPH
Vice Dean, Research and Graduate Research Education
Chair, Biomedical Sciences
Cedars-Sinai Medical Center
Los Angeles, California

FDA PARTICIPANTS (Non-Voting)

Issam Zineh, PharmD, MPH
Director
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS)
CDER, FDA

Shiew-Mei Huang, PhD
Deputy Director
OCP, OTS, CDER, FDA

Rajanikanth (Raj) Madabushi, PhD

Team Leader

Guidance and Policy Team

OCP, OTS, CDER, FDA

Martina Sahre, PhD

Policy Lead

Guidance and Policy Team

OCP, OTS, CDER, FDA

Kellie Reynolds, PharmD

Deputy Director

Division of Clinical Pharmacology IV

OCP, OTS, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. TERZIC: Good morning, everyone. As customary, let me ask you all to please silence your cell phones, smartphones, and any other devices if you have not already done so. I will also like to identify the FDA press contact, Amanda Turney. Amanda just stood up. You can see here in the first row over there.

At this point, let's go through the customary introductions. My name is Andre Terzic. I'm the chairperson of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee. I will formally now call the meeting to order of the Pharmaceutical Science and Clinical Advisory Committee for May 7, 2019. We will start by going around the table and introducing ourselves. Let's start down on my right.

DR. DONOVAN: Thank you. Good morning. My name is Maureen Donovan. I'm a professor of

pharmaceutics from the University of Iowa.

DR. SUN: Duxin Sun, professor in pharmaceutical science at the University of Michigan and director of Pharmacokinetics Core.

DR. FINESTONE: Good morning. I am Sandra Finestone. I am the consumer representative.

DR. COLLINS: Good Morning. Jerry Collins. I lead the developmental therapeutics program at the Cancer Institute at NIH.

DR. KRAFT: Walter Kraft. I'm a professor of pharmacology medicine at Thomas Jefferson University in Philadelphia.

DR. THADHANI: Good morning. Ravi Thadhani, nephrologist and vice dean of research at Cedar Sinai, Los Angeles.

DR. NACHMAN: Good morning. Patrick Nachman. I'm professor of medicine and nephrology, University of Minnesota, Minneapolis.

DR. NOLIN: Good morning. Tom Nolin from the University of Pittsburgh. I'm an associate professor in the School of Pharmacy.

DR. DOWLING: Good morning. Tom Dowling,

professor of pharmaceutical sciences and assistant dean for research, Ferris State University, Grand Rapids, Michigan.

DR. TENJARLA: Good morning. Srini Tenjarla, global head of drug product development at Takeda Pharmaceuticals, based in Boston.

DR. COOK: Jack Cook, clinical pharmacology, Pfizer, currently located in Groton, industrial representative.

DR. AWNI: Walid Awni, vice president of clinical pharmacology and pharmacometrics at AbbVie. I retired at the end of 2018, and I'm consulting right now.

DR. ZINEH: Good morning. Issam Zineh. I'm the director of the Office of Clinical Pharmacology at the FDA.

DR. HUANG: Shiew-Mei Huang, deputy director, Office of Clinical Pharmacology.

DR. MADABUSHI: Good morning. Raj Madabushi, team lead for guidance and policy in the Office of Clinical Pharmacology.

DR. SAHRE: Good morning. Martina Sahre,

policy lead in the guidance and policy team, in the Office of Clinical Pharmacology.

DR. REYNOLDS: Kellie Reynolds, Office of Clinical Pharmacology.

DR. SLATTUM: Patricia Slattum, professor emeritus of pharmacotherapy and outcome science, Virginia Commonwealth University.

DR. PAI: Good morning. Amit Pai, associate professor of clinical pharmacy, University of Michigan.

DR. SLUD: Eric Slud. I'm a statistician at the University of Maryland and the Census Bureau.

DR. LI: Good morning. Tonglei Li, professor of industrial and physical pharmacy, Purdue University.

DR. BERINGER: Paul Beringer, professor of clinical pharmacy at University of Southern California.

DR. MORRIS: Ken Morris. I'm a university professor at Long Island University's College of Pharmacy and director of the Lachman Institute for

pharmaceutical analysis.

DR. CARRICO: Good morning. I'm Jeff Carrico. I'm the service chief for clinical pharmacy and investigational drug research at the NIH Clinical Center, Department of Pharmacy.

DR. FAJICULAY: I'm Jay Fajiculay, designated federal officer for the Pharmaceutical Science and Clinical Pharmacology Advisory Committee, FDA.

DR. TERZIC: Thank you all. I think it's wonderful to see a very diverse set of fixed parties around the table, as we will be following up with important topics today. I will read now the statement at the beginning of each of the meetings.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder,

individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive and constructive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

The next point is to actually pass it to Dr. Jay Fajiculay, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. FAJICULAY: The Food and Drug

Administration is convening today's meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees

who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

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

Today the committee will discuss the following topics: 1, approaches to evaluate the effect of renal impairment on drug exposure; and 2,

best practice considerations for translating pharmacokinetic information into dose individualization instructions.

Regarding topic 1, many registration trials exclude patients with advanced kidney disease, and product labeling dosing instructions for these patients are commonly derived from our understanding of the change in the PK in individuals with varying degrees in renal function.

The most common current approach to determine dosing instructions for patients with varying degrees of renal function begins with a stand-alone renal impairment study, either full design or reduced design.

In addition to stand-alone renal impairment studies, drug development programs often use the findings of population PK analyses, which leverage the PK information across all studies available in a drug development program. An alternative approach to consider is for drug development programs to predict the impact of renal impairment on the PK of the drug, either based on the

understanding of the PK of a new molecular entity or using physiologic-based PK models without a stand-alone renal impairment study.

Patients with impaired renal function can then be included in later stage clinical trials with prospective dose adjustment incorporated if deemed necessary based on the predictions. The dosing should be confirmed based on analysis of PK samples from the late-stage trials such as sparse PK and population PK analysis.

Regarding topic 2, dose individualization is typically achieved by applying the concept of exposure matching under the assumption that such a maneuver will result in a benefit-risk similar to that observed in the registration trials.

The committee will discuss the application of exposure matching, including the necessary assumptions and any limitations. This is a particular matters meeting during which general issues will be discussed. Based on the agenda of today's meeting and all financial interests reported by the committee members and temporary

voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Walid Awni, Jack Cook, and Srini Tenjarla are participating in this meeting as nonvoting industry representatives, acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company. Dr. Awni is an independent pharmaceutical consultant. Dr. Cook is employed by Pfizer, and Dr. Tenjarla is employed by Shire Pharmaceuticals.

With regard to FDA's guest speaker, the agency has determined that the information to be provided by the speaker is essential. The following interests are being made public to allow the audience to objectively evaluate any

presentation and/or comments made by the speaker.

Dr. Richard Graham has acknowledged that he is an employee and shareholder of Theravance Biopharma. He is also affiliated with the International Consortium for Innovation and Quality in Pharmaceutical Development. In addition, his spouse is an employee and shareholder of Gilead Sciences. As a guest speaker, Dr. Graham will not participate in committee deliberations, nor will he vote.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topic that could be affected by the committee's discussions. Thank you.

DR. TERZIC: Thank you very much. We will now proceed with the FDA opening remarks, and I would like to recognize Dr. Kellie Reynolds, who will provide the introductory remarks on behalf of the FDA.

FDA Introductory Remarks - Kellie Reynolds

DR. REYNOLDS: Good morning. I want to welcome everyone who will participate in the discussion today, including all of the observers. As we begin the FDA presentations, I will provide some context about the topic and our rationale for bringing it to the advisory committee for discussion today, and other speakers will provide more details on the topic.

A simple way to state the topic for today is evaluation of subjects with renal impairment during drug development, including their participation in phase 2 and phase 3 efficacy and safety trials; however, the topic should be considered in a wider context.

During drug development, the inclusion of a broad patient population in clinical trials helps

provide evidence regarding the safety and effectiveness of the investigational drug and the full range of patients likely to use it if it is approved. However, the inclusion and exclusion criteria for the trials may prevent this. Some groups may be left out, such as those with impaired renal or hepatic function or certain age groups.

We want to use the outcome of today's discussion to take another step towards the generation of evidence that a drug will be safe and effective in the full range of the target patient populations. As you'll hear from the presentations today, this topic has been discussed at previous advisory committee meetings over the past two decades, so why are we discussing it again?

First, let's consider the context of the healthcare scenario. The economic burden of chronic disease is substantial. The cost of treating patients with chronic conditions account for 90 percent of the nearly $3 trillion spent on healthcare in the United States each year, but predicting drug response is a game of chance.

It's difficult to predict who will respond to many treatments for chronic conditions. For example, Brian Spear and colleagues surveyed response rates for approved drugs in several major disease areas and found wide ranges and responses, depending on the area, but many were less than 50 percent.

The low response rates may, in part, be due to challenges related to the multitude of intrinsic factors such as organ dysfunction or age and extrinsic factors such as drug interactions and diet that affect the risk-benefit balance in different patients.

The current regulatory environment provides additional incentive to consider how we evaluate patient groups during drug development. PDUFA V, which went into effect in 2013, included elements related to strengthening regulatory science. This emphasis was extended with PDUFA VI in 2018, adding language related to the use of innovative tools during drug development.

In its current state, there's a tension in

drug development related to the exclusion versus inclusion of patients with renal impairment in clinical trials. The rationale for exclusion may include minimizing heterogeneity in the clinical trials and reducing safety risks. The rationale for inclusion is to generate more generalizable data.

Under the current paradigm, which you will hear more about today, dosing instructions are typically based on our understanding of changes in drug pharmacokinetics with varying degrees of renal function. The pharmacokinetic data are collected in dedicated renal impairment studies or through population pharmacokinetic analyses of all available data from development programs. However, there may be minimal data available for some patients with severe renal impairment or end-stage renal disease, and the current program is really a retrospective one.

Now I'm going to go through the questions that we are asking the committee to discuss today. The first discussion item is please discuss what

alternative drug development paradigms would encourage the inclusion of patients with all or most degrees of renal impairment in late-stage clinical trials, without the need for a stand-alone renal impairment study, and the advantages and disadvantages of these paradigms as compared to the current paradigm.

You will also today hear a summary of some translation approaches. The evaluation of the effect of renal disease focuses on the effect on drug clearance and the resulting changes in exposure. Study results must be translated into dosing instructions for various patient subgroups. Doses are typically determined based on exposure matching to subjects with normal renal function.

We have three discussion questions related to translation. First, please discuss if it is reasonable to assume that a drug's exposure-response relationship will usually not be significantly different between patients with impaired renal function and patients included in the registration trial, and the situations where

the assumption of a similar exposure-response relationship may not apply.

Second, often for exposure matching purposes, the normal renal function group serves as the reference group. We propose the reference group be selected based on the understanding of benefit-risk for the drug and be more proximal in terms of renal function, for example, severe versus moderate instead of severe versus normal. Please discuss the pros and cons of this approach.

Finally, there are multiple approaches for establishing an exposure match. It can be matching based on a point estimate, confidence interval based approaches, exposure matching the 5th and 95th percentile, and there are others. Please discuss the criteria for choosing one approach over another.

Depending on your perspective, the task ahead today may seem either simple or complex, but I propose that it's both. As stated by Alan Perlis, "Fool's ignore complexity, pragmatists suffer it, some can avoid it, and geniuses remove

it." By the end of the day, I hope we achieve the second statement, "Simplicity does not proceed complexity but follows it." So I hope we walk out with a simple approach to this complex problem.

That concludes my opening remarks. Dr. Martina Sahre will now provide information about the current paradigm for evaluating the effect of renal impairment during drug development.

FDA Presentation - Martina Sahre

DR. SAHRE: Good morning, everyone. After Dr. Reynolds so nicely introduced the topic just now, I will go into what we consider to be the current paradigm for the determination of dosing instructions for patients with renal impairment.

Briefly, I will just orient ourselves to the history of guidances and how patients with renal impairment are enrolled into clinical trials, and also relate that to the prevalence of chronic kidney disease, and then go into the current approaches to generate data and how that then translates to the information content that we have for dosing and renal impairment in our labels.

First as an introduction, the FDA published its first renal impairment guidance in 1998, really underlining the importance of assessing the impact of renal impairment on drug exposure at some point during the drug development program. In that guidance in '98, we laid out our current thinking at that point in time on when and how to conduct that study and translate that into labeling.

Then 10 years later, we had advisory committee meetings to talk about issues that had been identified at that point in time that needed to be addressed. And in this case, we talked about the impact of renal impairment on the non-renal clearance routes, i.e., metabolism and transporters, including biliary clearance.

That culminated in the publication of our draft guidance that was published in 2010, where we expanded the section of renal impairment on non-renal elimination. We added monoclonal antibodies to a list of scenarios where you would not require a renal impairment study. But then also, we included the modification of diet in a

renal disease equation to estimate eGFR, which is not the purpose of today's meeting discussion.

Now that it's been almost 10 years since the last time we had an advisory committee meeting and the last time we have updated our guidance, now is a good point in time to step back and discuss what new topics need to be addressed in order to provide dosing instructions and labeling for patients with renal impairment.

To that end, I'm going to just pause at a very common observation that we've all made, and that is that patients with renal impairment are often excluded from clinical trials; then the corollary is that that can result in gaps in labeling for these patients.

Why do I say that they're often excluded from clinical trials? When trying to assess the literature that is out there on how patients with renal impairment are included in clinical trials, there is not exhaustive data, but there are some journal articles that treat the enrollment of patients into cardiovascular clinical trials.

There is one literature review paper by Konstantinidis and others that looked at cardiovascular trials for heart failure in coronary disease that were published between 2006 and 2014. They identified, based on the criteria that they had, 371 trials out of which roughly 60 percent excluded patients with kidney disease.

In the majority of these cases, they excluded -- in about half of these cases that were excluded -- based on serum creatinine, and that creates a serum creatinine that was outside the upper limit of normal range.

In 25 percent of cases where exclusion criteria existed, they excluded based on glomerular filtration rate or creatinine clearance, and in this case less than 30; so that would include patients with CKD stages 4 and 5. Some are also excluded for renal replacement therapy or just had a non-specific language for that.

The topic of inclusion and exclusion criteria was also the topic off of a workshop that was held last year here in downtown D.C. For that

workshop, there was a presentation on renal related exclusion criteria that one of our colleagues from the FDA made, and they presented a retrospective non-random sample of 38 clinical trials that was assessed for exclusion criteria, and they found that roughly 80 percent of these trials, of these 38 trials, had exclusion criteria related to renal disease; 60 percent excluded based on creatinine clearance or eGFR, and also based on serum creatinine.

If you note in the little box below, it says that about half of them excluded based on creatinine clearance, and that the majority used a cutoff less than 60 milliliters per minute. So they also excluded patients with moderate renal impairment.

In a slightly more comprehensive analysis of new molecular entity approvals that were from 2016 to 2017, colleagues in OCP assessed the submission packages for these 67 new molecular entities for their late-phase trials and the exclusion-inclusion criteria in these late-phase

trials for renal related exclusion criteria.

They found that 47 of the 67 new molecular entities had exclusion criteria based on renal disease and that roughly half of them excluded based on eGFR or creatinine clearance, and slightly less than half excluded based on serum creatinine or the existence of renal disease.

Thirty percent had no exclusion criteria listed, so they were just assumed to be free to enroll these patients if they appeared on the doorstep of an investigator. Now that we've seen that in roughly 60 to 80 percent of cases, there are some exclusion criteria based on renal disease, so what is the population of patients with chronic kidney disease out there?

This data comes from the United States Renal data system from their 2018 annual data report. In that report, they report the prevalence of chronic kidney disease in the United States to be about 15 percent in the adult population. That could be as many as 30 million people, probably slightly more, so it's a sizeable population.

We know that comorbidities are common in this population, and comorbidities are usually treated with direct treatment. It would be nice, for these populations that are typically not included in trials, to have some form of a dosing recommendation. Note, though, that the vast predominance of patients in CKD are in stages 1, 2, and 3. Stages 4 and 5 make up less than 1 percent of that entire population, so that already highlights a bit of a challenge for how to assess any drug in these patients.

Moving on, under our current paradigm, in a very high-level summary, we actually obtain the data that is used to derive labeling. Our current draft guidance, the 2010 draft guidance, which is still the current applicable guidance, recommends a stand-alone renal impairment study when the pharmacokinetics of the drug is likely to be influenced by renal impairment.

The guidance states that that's the case when you have a drug that is excreted up to 30 percent or more into urine as unchanged parent

drug. We also think that when the drugs are eliminated predominantly by non-renal routes, there is the assumption that metabolic and transport pathways could be affected by renal impairment.

The design of these stand-alone renal impairment studies is often referred to as full design versus reduced design. A full design refers to the enrollment of participants that present the whole spectrum of renal function. That is outlined in the table on the right, which can be used to enroll patients into these stand-alone renal impairment studies. However, patients with kidney failure are usually not enrolled into these full design studies.

The reduced design study is a concept for studying the impact of renal impairment on PK for drugs, where non-renal clearance routes predominate and where the idea is to test a worst-case scenario in a population that has highly reduced renal function.

The 2010 draft guidance stated that that should be end-stage renal disease patients who are

not yet on dialysis. However, at the advisory committee meeting that was held I think on the same day that the 2010 guidance was published, there were many stakeholders that told us that this is essentially a population, that for the purpose of conducting these stand-alone renal impairment studies doesn't exist; also, the severe renal impairment group could actually approximate a worst case just as well as these end-stage renal disease patients who are not yet on dialysis.

The current thinking within the office, and I think the current practice, has been to recommend to enroll severe renal impairment patients; so just to highlight that this is slightly different from what it currently says in the guidance.

That 2010 draft guidance also refers to the use of data from phase 2 and phase 3 studies because sparse PK samples are often collected, as we've already heard, and then these data are obviously used for downstream analyses. Both the sponsors and the agency will typically do a population PK analysis or other analyses to assess

for covariate effects of which renal impairment could be one, and then calculate or assess exposure metrics of interest for a particular program.

Obviously, these data can then also be used for analysis of exposure-response in relationships, and I will refer to Dr. Madabushi's talk because he will go further into that topic.

So now that we have all this data, how does that translate into the information content with regard to how to dose these patients in labels? What we did to understand how the data translates to labels is we looked at approvals from the last 3 years of approval, from 2016 to 2018. There were 127 total approvals, and out of those, we looked at a 115 labels; 33 of them were BLAs and 82 were NDAs, and we parsed these labels for information regarding dosing in patients with renal impairment.

We would look at the sections that would typically include that, which would be the dosing and information section, the specific population section, and also the clinical pharmacology section. We coded everything as dose information

when there was either a clear statement of how to adjust the dose, i.e., reduce dose X to dose Y to treat in this particular patient population, or if it said that clearly for renal impairment, there is no dose adjustment needed, when it said to avoid use, it's contraindicated, or any such statement.

We code it as no information when the label essentially said there was either no study conducted, or the impact of renal impairment is unknown, or we just can't provide you a dose in this particular group. And that was most often the case for the severe and renal failure groups, and that for mild and moderate disease of which population PK analysis suggests that there is no impact on the drug PK, but because severe renal impairment wasn't studied, we can't give you a dose for that in particular.

So that was labeled as no information. In very rare cases, there was also no section 12 regarding renal impairment at all.

When we look at the bar charts on the left, what we can see is that for mild to moderate

disease, we usually include some -- our labels usually include dosing information for patients. However, that drastically is reduced for the severe renal impairment patients and also for the renal failure groups, for various reasons obviously. So there is work to be done and there are gaps that still exist.

In summary, we've heard that these patients are often included, but it seems to us that in the clinical scenario, or in the clinical setting, a patient might need a drug even if it hasn't been studied in clinical trials in the renal impairment population or in the kidney disease population.

Unless there's really a mechanistic or a safety reason not to, these drugs might be used in these patients, and therefore, it might be useful to have these dosing instructions in these labels. Clinical pharmacology attempts to fill these gaps that currently exist by providing dosing instructions based on these dedicated renal impairments studies into phase 2 and phase 3 information, but there are obviously still gaps

that remain.

So where can we go from here? We often hear that the renal impairment studies are done relatively later during the development program, so there should be a lot of information that is available early about the drug that could be potentially utilized in more efficient ways, or it might actually contain more information that we currently use to anticipate altered exposures to then facilitate the enrollment of these patients into phase 2 and phase 3 trials. But there are obviously potentially many other approaches to be taken, and that is part of the discussion question, the first discussion question that Dr. Reynolds just read.

With that, I'm going to hand the presentation over to Dr. Madabushi to talk about the translational aspects.

FDA Presentation - Rajanikanth Madabushi

DR. MADABUSHI: Good morning, everyone. Thank, Dr. Sahre.

On the next few slides, I will set up the

background for discussion for the second topic that is translation. Irrespective of how the information is collected, almost always, there exists a situation that needs translation of the information developed from the drug development program into the labeling. To that end, our existing guidances over a period of time have laid down certain fundamental principles to achieve that, which I have listed here, and I'll briefly go over.

Typically the development of dosing recommendations is based on understanding the relationship between some measure of renal function and how it relates to a relevant pharmacokinetic parameter of interest, which could be the area under the plasma concentration time curve or a measure or an estimate of clearance, which could be a total clearance or a renal clearance estimate, and the half-life of the drug. These relationships help inform the translational aspect from information to dosing.

An understanding of dose-exposure-response

relationships, whether it be for the efficacy or for the safety, can often be useful in assessing or identifying a particular subgroup of interest, whether it warrants dose adjustment, and if so, what type of dose adjustment would be required.

Eventually, all this information boils down to deriving of the doses, which is usually either a dose reduction, or extending interdosing interval, or a combination of both. This is derived based on the fundamental concept of exposure matching, and this exposure matching is done with respect to a reference group of interest.

Often the subjects with preserved or normal renal function are considered as the reference, and it is this particular concept of exposure matching, which we are bringing for discussion today, which I will go into further details.

There are several key considerations for exposure matching. I'll go ahead and talk about these three key considerations over the next few slides. It's about the assumption of similarity of exposure-response relationship, how one goes about

choosing a reference group of interest, and how to establish an exposure match. These are the three critical aspects of exposure matching, and I will go into details about each one of these.

What is this concept of similarity of exposure-response? I'll use this concept to go through what I mean here. I'm showing here a plot on the X-axis, an exposure measure drug concentration, and on the Y-axis an axis for the response. The blue curve here is showing the relationship between exposure and efficacy response measure, and what I'm showing you here is a classic sigmoidal curve. One could also expect a similar type of relationship for a clinically active moiety to exist for the safety event of interest, which I'm showing you here in the red for the safety event of interest.

Based on the clinical experience and the target population, or let's say even for subjects with normal renal function or preserved renal function, the box plot is expected to represent the range of exposures wherein a drug would be seeking

approval at a given dose level. So if one were to look at this on the median of the box plot, and if we draw a vertical line, clearly there is a good expectation of efficacy and very low risk for safety. So clearly the benefit-risk exists here.

Let's say someone did a renal impairment study based on the expectation, what doctors described, and the observation was their exposures in that particular study was projected to be 2-fold increase in exposure, which I'm showing in the box plot towards the right here.

Under the assumption that the exposure-response relationships both for the efficacy, the blue curve, and the safety, the red curve, are same for both the reference as well as the renal impairment group, one would anticipate a higher incidence of safety events at the exposures that are expected in these renal impairment subgroups.

Obviously, this would warrant a need for some kind of adjustment so as to achieve the benefit-risk, which was observed in the late-phase

clinical trials and the reference group of interest, and that's usually done by reducing the dosing or adjusting the inter-dosing interval such that the whole exposure range is moved to match with that of the reference.

In this situation, you can see the safety would be mitigating; such like by exposure matching, under the assumption of similar exposure-response relationship, the benefit-risk of this unstudied group of patients in the late-phase clinical trials, one could derive a dosing to achieve a similar benefit-risk ratio.

However, there are no guarantees that this relationship is expected to be similar always. One could envision different scenarios where this could be different. For example, I'm showing you here a situation where the renal impairment subgroup might be less sensitive to the treatment effect such that the EC50 is moved to the right, and they may require higher exposures to achieve similar effects as what was observed in the reference group.

We have observed this kind of phenomena for

the sodium glucose co-transport inhibitor situation, where clearly the glucose excretion rate decreases with the worsening of the renal function, for example. In this situation, if we were to assume that the exposure-response relationships were similar and if we did an exposure matching to match with that of the reference group, the benefit-risk would be altered. This subgroup would have a lesser benefit compared to that of the reference group.

On [indiscernible] project, a slightly different scenario where the patients with kidney disease or impaired renal function are more sensitive for safety events. We have seen this reported for other anticoagulants where patients with kidney diseases are at a high risk for bleeding with anticoagulants.

In this situation, even though the dose adjustment to achieve the exposure match would be done to match for the safety, it would still result in a higher safety event of interest and would not achieve the primary goal of exposure matching, that

is to achieve the same benefit-risk.

These are just two hypothetical situations, where we have some experience alluding that this can happen, but there could be a number of combinations of these happening where the exposure changes and the safety also changes, and any of the combinations that can be thought of.

Some of the challenges here are that there are no clear criteria when these assumptions can be considered acceptable. That is the concept of similar exposure-response relationship between the normal renal function and those with impaired renal function. The compound to this problem, based on what Dr. Sahre presented, most of the time, patients with impaired renal function are excluded from the late-phase trials, which are the sources for characterizing the exposure-response relationship.

So there is no way of knowing whether this assumption is true or is it violated. In situations where it is violated, our exposure matching may not be doing the job we thought it

would do, and it may require some accounting for the underlying exposure-response relationships across different groups. This is one of the topics that we are bringing to the committee to get your insights on; how can we go about establishing best practices and understanding when this assumption could be true, and when it may be altered, and how we can go about resolving the situation.

The second aspect related to the exposure matching is the choice of the reference group. If you look at the 2010 guidance, it says it could be subjects with normal renal function, and I will walk through what that concept means in this table here.

The first column would be the range of renal function categories that would be studied in a stand-alone full design study, ranging from normal to severe typically. The second column shows the findings of that particular study relative to normal renal function such that subjects with mild impairment have a 30 percent increase, moderate have a 50 percent increase, and

severe impairment are demonstrating a 2-fold increase. When we look at the phase 3, which is the late-phase trial, patients with normal to moderate impairment were included and studied at the doses, which they would be seeking a approval or labeling provided that the benefit-risk was acceptable in general.

For determining the dose adjustment for the severe renal impairment group, one would use the factor that is observed in the stand-alone study, that is a factor of 2-fold, and compute a dosing that will be halving of the dose of 50 milligrams. This is what would be if one were to choose reference subjects as normal renal function based on the renal impairment study.

However, clinical trials often include patients with mild impairment and in some situations moderate impairment. In this hypothetical example, there was clinical experience up to moderate impairment, and that is an opportunity to utilize this particular clinical experience to better inform the choice of renal

impairment, and what some of the concentrations could be.

For example, the 2010 draft guidance says for drugs with wide therapeutic range, subjects with normal function and mild impairment can be considered as a reference. However, it is very difficult to establish during a drug development program what is the therapeutic range and whether it's wide or not. When exposure-response is available, the choice of this reference group could be informed, but this is still a retrospective procedure, and often there is not enough information that is available.

In the absence of such information, maybe one thought is to choose a group for reference with an acceptable clinical experience that is more proximal in renal function to the subgroup of interest. For example, based on the previous hypothetical where normal to moderate was studied and severe were excluded, the proximal group there would be moderate renal impairment, and if that clinical experience was acceptable, maybe that

could be used as a reference such that you have very gradual dosing recommendations as opposed to choosing normal renal function. There could be pros and cons to it, and that's the second of the topics under this topic 2 of translation that we are seeking your input.

Lastly, the establishment of exposure match, how does one go about it? This concept is not unique for renal impairment. In fact, this applies to all of the clinical pharmacology applications here, and if you were to look across all our guidances and our practices across intrinsic and extrinsic factors, we come across several different approaches of establishing exposure match, which I'll go one by one here.

Starting with matching to the point estimate, here the dosing is derived based on the group mean or an estimation of the geometric mean ratio, which is often from the stand-alone study. This example is very similar to what I described under the choice of the reference here.

For example, this was the finding of a

stand-alone renal impairment study across the categories of renal function, and the geometric mean ratio is computed relative to the normal such that here mild a 30 percent increase, moderate is 2-fold, and severe impairment has 4-fold increase.

In this situation, if we assume both normal and mild were studied in the late-phase trials, how would one go about deriving dosing for moderate and severe? It would be simply applying these factors of 2 and 4 and computing doses which are half and quarter, and this could translate into labeling of something of this nature wherein a 2-fold increase was observed in this subgroup of moderate impairment. To maintain similar systemic exposures of the drug of interest, the recommended dose is decreased by half and so on and so forth. This is a concept of matching to the point estimate.

The second approach, which we have mentioned in our latest draft guidance for the clinical drug-drug interactions, which is matching the confidence intervals to a predefined, no-effect boundary, and I will explain how this goes about.

This is a graphical representation of the finding, which I showed in the table in the previous one, almost similar to that. So you can consider this as just a pictorial representation, not a tablet presentation. On the X-axis you have an estimate of the geometric mean ratio, which is derived using normal renal function as the reference.

So that line of would represents your normal renal function, and the point estimate and 90 percent confidence intervals are computed for each of the groups.

Based on the understanding of the information that is available in the drug development program, on an average a no-effect boundary could be computed, and that would be useful in trying to understand or identify groups that may warrant dose adjustment. For example, in this situation, clearly, subjects with mild impairment do not require any dose adjustment because they are clearly falling within this no-effect boundary. We think these exclusions are

acceptable and do not significantly alter our perception of benefit and risk.

However, dose adjustment would be required for both moderate and severe, and then this collapses to almost like a point estimate, but it takes into account the confidence intervals, and the dose adjustments would be expected here in the red on the right to provide the exposure such that they fall within the no-effect boundaries and does establish the exposure match and derive the dosing instructions.

The last of these approaches is matching to a range of exposures observed in the clinical trial. This approach has been utilized predominantly in the pediatric domain, and I will explain how this is different from the first two approaches.

Here is the information let's say from a late-phase trial. On the X-axis is the renal function presented in a continuous manner going from 120 to as low as it is available, and on the Y-axis is the area under the plasma concentration

time curve. The black dots here are the exposures observed in the late-phase trial. This could be derived from popPK, whichever approach, but this is the range of information that is available from the phase 3 studies. Clearly, you can see patients with moderate impairment or severe impairment are excluded. It's missing here because they were excluded, and that information is not available.

Based on the understanding of the exposure-response relationships, and even the benefit-risk understanding in this particular situation, one could posit intervals almost similar to the no-effect boundaries, but now this is on the range. For example, I'm showing you here 5th and 95th percentiles of this particular experience as being acceptable.

This is listed as an example in our pediatric clin-pharm guidance. People have used different approaches. One could use interquartile ranges or depending upon how comfortable we are with the information that is available. Once this is set, we could now overlay this with the findings

of the stand-alone study in a continuous manner, which I'm showing you here with the diamonds here, and one could actually characterize the underlying continuous relationship across this entire spectrum of the renal function, which can then be used to inform what are the thresholds beyond which dose adjustments are required, and how much of a dose correction is required.

This approach is typically used to identify the body weight bands for dosing in pediatrics. Something like that could we envisioned. For the purposes of this illustrative example, I have provided here a threshold at 40 mL per minute and start off the expected 30 mL per minute, if one were to grow by the categories of normal, mild, moderate, and severe, as a justification for dose correction. The projected exposures could be simulated and could be compared to see how that range compares to this range that is established.

In summary, translation of findings from stand-alone renal impairment studies to dosing for renal impairment subgroups that are excluded from

clinical trials often rely on the concept of exposure matching. There are several considerations for exposure matching. The most critical one is the assumption that the exposure-response relationships for both efficacy and safety between the reference group and the subgroup for which dosing is derived is assumed to be similar. More often than not, the choice of the reference group has been reverted to patients with normal renal function.

We also saw several different approaches to establishing the exposure match, which can result in different dosing instructions. Clearly, there is a need for good criteria and best practices on how we go about addressing these considerations to translate the dosing.

Before I go ahead and take any clarification questions, we would like to acknowledge a lot of individuals who contributed to developing these concepts and informing us, bringing these topics to the committee. Thank you very much.

Clarifying Questions to Presenters

DR. TERZIC: Thank you very much. Actually, thanks to all the speakers from the FDA for very nicely presenting and framing the questions. We do have some time for clarifying questions, and this is important to the FDA as they continue to work on this subject. So the floor is open. Please recognize yourself and the institution from where you come.

DR. MORRIS: Ken Morris from Long Island University. Just one question that occurred to me. In the clinical trial data that's available -- this may not be available, or hypothetically -- does the order of elimination change with renal impairment, or is there any knowledge about that?

DR. SAHRE: Can you clarify what you mean by order?

DR. MORRIS: Changing from a first order, where you can actually get a half life, to zero order or some other order. Do we know -- is it just the rate that changes or is it possible to change the order of elimination as well, the

pharmacokinetic order?

DR. SAHRE: Yes.

DR. MADABUSHI: Generally, the order is not expected to change, especially when we are thinking of glomerular filtration rate as one of the primary determinants here. It's generally the first order process. So generally, that's not the situation, so the underlying assumption here would be the order is not changing.

DR. MORRIS: Thank you.

DR. COOK: Jack Cook, industrial representative.

Raj, I'm not going to let you get off that easy, because I haven't done this. Have you looked to see if variability increases with the more severe groups? Your nice presentations were pretty clean there. I like those approaches. The problem is that my bias is that's more variable just in the way we measure creatinine clearance.

The ones that take into account the range of the confidence interval get a lot harder to do because you could envision even the case where that

group, where you try to stay below some no-effect dose, that having less of an adjustment because of wider bands than maybe a group not as severe.

DR. MADABUSHI: I think there were two parts to it. One is do we expect the variability to also be a function of renal function. In general, based on our experience, we see that with the worsening of the renal function, the variability does increase, and probably that's also a byproduct of the renal function that is also fluctuating on any given day, even though we expect it to be stable. But we have, in general, 10 mL per minute as a standard deviation. That's one aspect. If we were to look at the stand-alone studies, the confidence intervals get wider as the categories become worse and worse.

The second question with respect to translation for exposure matching, could you repeat that question?

DR. COOK: In slide 40, if you can bring that up. That bottom bar, when I slide that over for the no-effect boundary, because it's so

wide -- in these studies, your colleague mentioned that it's actually sometimes hard to find enough patients to get that. To reduce that confidence interval, you may have to slide it so far to be below the no effect, that it actually has less of a change from the mild group than maybe the moderate, which has a tighter confidence interval.

DR. MADABUSHI: Sure. Some of these corrections, when you start doing it for these groups, if we are using normal as the reference, that does give this inverted U-shape kind of relationship or it appears that way. The hope would be to have as much as the confidence interval covered within the no-effect boundaries as opposed to the entire shifting below and can pass between that.

That would be the process there. But you're right. The same thing could also happen for the point estimate matching also, wherein suddenly the group will have lower exposure. That's one of the things.

DR. TENJARLA: Srini Tenjarla, industry

rep. Thank you. I think it was a very good presentation from the agency there. I just have a question. During the review of all the dossiers on your end that you presented, 300 something, was there any attempt made to correlate with any kind of preclinical data on modeling in terms of renal impairment, or it usually is very difficult to get that kind of information early on?

DR. SAHRE: I would just like to clarify that that 300 some trials, that was a literature review. That was a paper that was written by someone else. I don't know. I don't think that they correlated that in any way.

For our analyses, I didn't look back to the preclinical data. We certainly could do an analysis that goes on to say whether or not there was more data related to when the drug was actually predominantly renally cleared or something. We haven't done this type of analysis yet, but I'm sure that could be done.

DR. TENJARLA: The reason I asked that question is I think many people in the industry

would like to do early PK studies, but one of the reasons why there is hesitation is because there is no clear regulatory path forward. So I think an opportunity to discuss early on with the agency on a certain plan might be helpful; otherwise, it might be a chicken and egg story here because you absolutely need the PK data early on. But if you don't do that because you're not certain of the regulatory approval process, people will just fall back up on what is the official guidance, which is basically do a stand-alone PK study separately, then we'll be going in circles.

DR. AWNI: Walid Awni, industry representative. I have a couple of questions. One of them is related -- I don't know if you looked at the number of applications at the FDA where there is this independent study to look at renal function and to see what percent of them actually included the full allotment of the severe renal impairment, because from my experience, we run these studies and then you finish the mild, moderate. Then you get to the severe, and you're having a hard time.

It's 6 months, 9 months say, and say, hey, we've got to go with submitting this information because the mild and moderate is that.

So it will be very helpful because it's really saying even in this independent study, it is not an easy task actually to include the number of subjects. That also adds to the variability question.

If you have a free subject with severe renal impairment, you have a very broad -- which makes it very difficult actually to make a very specific recommendation on those individuals. I don't know if you have looked at it that way.

To Dr. -- in my experience, this is a safety issue. Is that a true statement from where you sit? It's really driven by our concern that with the severity of renal function, we are putting human beings at a higher risk if we give the same dose. From a safety-efficacy point of view, if they have better efficacy, that's fantastic. If they have the same efficacy as patient, usually you have this a wide variability, in the disease state

anyway, and you don't know is it renal, is it really this patient, just their response.

So I don't know if you -- it will be fantastic, actually, to look and to see if there is an ability to go back and look and see what are the cases where the efficacy was different. There are examples, and you gave very good examples. So I wonder if you had looked at it in your own data.

DR. MADABUSHI: Sure. To answer your question, we have not looked at it in that particular perspective, whether it was a safety or an efficacy kind of an issue. You're correct in that there are experiences, not that huge, when it comes to efficacy aspects, but we do come across them. That often raises the question is there also underlying efficacy related that should be looked at.

But more often than not, when we are translating the stand-alone PK studies to dosing, we are looking at it from a primarily safety perspective. That's what we are doing. We think this is a fundamental clinical pharmacology aspect

that can be addressed. If that can be addressed post-approval, obviously there could be ways to achieve that during development also, if there are ways to go about it. That's what we would like to hear, how we can get there to get that clinical experience, which will help us inform this implicit assumption that efficacy is not an issue here; it's only the safety, and what we are doing is the right thing. That would be useful.

DR. TERZIC: Dr. Thadhani?

DR. THADHANI: Thank you for the presentation. One parallel group that we can perhaps learn from, although not exactly the same, would be those individuals with liver disease. If one looks in that population and asks the question, what types of approaches have been used that perhaps can inform us, again, understanding there may be differences, what can we learn when this kind of experience has been examined in that population?

DR. MADABUSHI: We do agree with you that there are shades of similarities, but in our

experience, we have heard that the liver diseases are a lot more complex, especially from a clinical pharmacology perspective compared to the renal disease.

At least on the PK aspects, there is a certain degree of clarity and expectation, and we do not have this underlying immunological aspects that are also existing in the liver disease kind of thing. But we are thinking some of the learnings from here would also apply there as opposed to that being our source for learning. That's the way we are thinking about. Others can jump in.

DR. KRAFT: Walter Kraft, Thomas Jefferson University. The discussion so far has been largely about exposure matching approaches to tackle exposure-response. I'm thinking about the label as a vehicle to communicate information to our end users, which are the practitioners. Have you thought about human factors in terms of information transmission to clinicians who will use this, particularly around -- I think there's some good literature about the innumeracy among

practitioners, myself included.

How does that come in terms of picking a particular methodology with how it would be represented in label?

DR. ZINEH: This is a great question that probably requires its own advisory committee. In fact, that was a major topic of our last one on drug interactions; what are the best practices in medical cognition that might help you translate drug interaction information into labeling?

I would say that is a work in progress. There's ongoing research on how to best to do that. We have been playing around with labeling enhancements that range from -- and this is not specific to renal impairment. This is really relevant to all of what we call intrinsic or extrinsic factors. There are some labels that actually show that.

I think one of the questions, going back to Jack's question to us, is what is specific about the therapeutic context that might create some nuance labeling that needs to be conveyed? For

example, when should you convey information about variability in response? That's captured, to some extent, in our clinical pharmacology labeling guidance, where we ask our staff, as well as the drug development side of things, to take a step back and say what do we know about the -- is there a threshold effect for efficacy or safety? What do we know about the exposure-response? Is the drug highly variable, and does that matter? Does outlier status need to be communicated if that's the case?

So there's not a neat answer to your question. I think that's just the million dollar question as it comes to translation of labeling for all of these intrinsic and extrinsic factors.

DR. TERZIC: Dr. Dowling, I believe you have been patient.

DR. DOWLING: Tom Dowling from Ferris State. Along the lines of exposure matching, we wrestled with this concept before of the wide therapeutic range. We're talking about do dose adjustments need to be made in a much more

concerning scenario where there's a narrow therapeutic range versus wide?

What is the FDA's thinking on what's the definition of a wide therapeutic range, or how are we moving into starting to categorize drugs into -- renal dosing is going to be more concerned, not only because the clearance is 30 percent or more by the kidneys, but also it's a narrow therapeutic range type of scenario.

DR. MADABUSHI: Sure. I don't want to use this cliche term, when we see it, we will know it kind of situation. But essentially, this concept of therapeutic ranges is informed by the experience during the drug development program. Definitely we have a better handle on what may constitute as narrow therapeutic range or an index kind of thing. We have published on those, which talk about the steepness of this exposure-response and things of that nature.

But generally, we are looking at the clinical experience that represents, I don't know, 2- to 3-fold of exclusions, wherein there were no

clinical, uh, events that were observed or had consequences such that they warranted some kind of mitigation approaches.

That was the challenge. If we knew them in advance, that it was wide enough, that makes it easier either to figure out whether a dose adjustment is needed or not, or if so, when and by how much. Maybe we don't need to half the dose in everyone all the time. I don't know. These all could come into the question.

It's almost a retrospective look. You look at the development program, and you get a feel for it as to what might be. And that also goes to informing these no-effect boundaries, concepts also, where how more certain we can be that these exclusions will be acceptable. The wider they are, people will be more comfortable in accepting them as having wide enough to predict range.

If you look back at the dosing instructions, they also give you some insights. There is no dose adjustment all the way up to let's say 30 mL per minute for a drug that is renally

cleared. One could infer, yes, it does have a certain range of exposures where the benefit-risk is reasonably acceptable.

I don't know if that answered your question, but it's always a retrospective look.

DR. PAI: Amit Pai, University of Michigan. My question relates primarily to this idea of when does that exposure match need to happen. In the perspective of anti-infectives, there may be that critical exposure period that's necessary for that first 24 to 72 hours. So you may compromise exposure in that match because you're thinking about that, basically achieving similar exposure to the normal group, where that safety issue may be more downstream. I think timing is also critical.

I'd like to hear your comments about that.

DR. REYNOLDS: Our thoughts on exposure-response and safety and efficacy are context specific. I agree for anti-infective type drugs where early exposure is important, that is something that we would think about. We would look at the entire dosing interval over the 7 days or

the 14 days. In some cases, if we were adjusting the dosing interval because of renal impairment, there may be a loading dose. So the exposure-response is considered for this specific disease state and drug.

DR. CARRICO: Jeff Carrico, NIH. The conversation seems to be going towards concentrations, and efficacy, and perceived outcomes, those types of things. If the consideration is to include more patients in clinical trials with decreased renal function, are there concerns or have there been considerations made for if the medication being given has renal toxicities associated with it, and if someone's renal function decreased further, basically?

DR. MADABUSHI: A simple answer is yes. If a drug is expected to have some renal injury as a mechanistic basis, definitely that goes into consideration. I think that's also one of the reasons why inherently there are exclusions. As renal function gets worse and worse in the patient population, there is the fear of unknown and what

might happen in these vulnerable patients. If there is an a priori expectation, that always features with respect to how the studies are conducted.

DR. TERZIC: Please?

DR. ZINEH: I'd just like to make a point, piggybacking on Jeff's comment. We're beginning to discuss importantly the trade-offs between doing one paradigm over another. I want to raise awareness that whatever you ask us, we're going to ask you back.

So that question around the trade-offs of including people that we otherwise wouldn't include in let's say phase 3 efficacy trials, there are a variety of challenges in doing that. You're trading off generalizability and representativeness against maybe some ambiguity on the back end when you're making prospective or proactive dose adjustments per protocol that at the end of the day, based on exposure-response, might be unnecessary.

This goes back to the question of

therapeutic range or where we are on the exposure-response curve. None of these that we've laid out are -- they all have their trade-offs, and I think it's hard for us to endorse any one approach, and it's also hard for us to be consistent with any one approach. That's really why I think Kellie's talk was titled, really, is there a need for a consensus approach on dealing with some of these issues?

DR. CARRICO: I think that's a very interesting point because the thing that comes to mind is we're talking about benefit-risk here today, and working with IRBs, I'm used to thinking about risk-benefit. So your trade-off to that point is I could see that if the paradigm is switched, then there's going to have to be a real paradigm switch in IRBs, as well, because including these patients could be seen as increasing the risk of the trial.

DR. AWNI: I was going to follow up with, if at least the division asks company to justify why they exclude patient in that group? Is it just

because we exclude severe renal impairment because we do want to -- is there justification? Do you ask for justification?

It's very important to say why are you taking such a decision. I remember -- and you probably -- including female in by-study, female in the first in-human study. Those are lots of argument, and back and forth, and moral questions, and all of that. But because you as an agency start asking that question, people will start justifying. There are lots of unique situations that with the overwhelming majority, that was really not a problem.

So are you asking right now for such -- like justify the criteria -- the renal criteria or exclusion based on the renal criteria?

DR. ZINEH: I think there's a growing awareness of inclusion and exclusion -- the justification for excluding certain populations from clinical trials. As Martina pointed out, there was a workshop on this last year that was a Duke Margolis FDA thing, where it was completely

dedicated to the question of inclusion and exclusion criteria.

You're starting to see trends in people asking that question. It's not just limited -- and there may be very good reasons to exclude patients from these trials, whether it be an issue of risk, whether it be an issue of reducing noise variability and increasing likelihood for seeing a drug effect if there is one. So there are very good reasons, and again, it's not just renal. You're starting to see lower age groups being enrolled in certain clinical contexts.

Whether that's done systematically, I think it's not, and if we identify some sort of rubric here, or begin to have that conversation around when you would want to see more of that done, I think we can operationalize that, but that's still an open question.

DR. SUN: Duxin Sun, University of Michigan; a question to clarify. In the current guidance for the stand-alone PK study renal impairment, do agents only ask for the drug with

30 percent renal eliminated drugs, or that's not defined, that could be also for non-renal eliminated drugs?

The follow-up question would be, you asked us to discuss the criteria. Do you want us just to focus on more than 30 percent renal eliminated [indiscernible] drugs, or you want to expand more?

DR. SAHRE: I think there is an understanding that non-renal routes can be impacted by renal impairment. As we understand more about what pathways are affected at what ranges of renal function impairment, there might be ways to make an argument as to why you might not need to do a study, but currently there is this going thinking that you should at least study in a severe renal impairment population kind of a worst-case scenario for whether or not your drug is affected.

Or you might also fall into a list of drugs or considerations where you might not have to do a renal impairment study. There are considerations listed. Say for example, your drug has a molecular

weight greater than 69 kilodaltons, or it's a single use, or it's a topical use, or some exclusions of that nature. In that case you wouldn't need to do a study but if your drug is predominantly renally excreted, you should.

DR. COLLINS: Jerry Collins, NIH. What we're really talking about is picking the starting dose for therapy, and I would think one of the issues we'd like to be concerned about is how good are we at doing that. We have all these different dosage adjustment schema.

Are there any data that say we have to make more adjustments when we use schema A than schema B? Is there any evaluation of how good is our strategy at picking the starting dose for the patient?

DR. MADABUSHI: Correct me if I'm wrong. I tried to rephrase it so that I understood better. There are two paradigms. One is retrospectively, you do the stand-alone study and you derive dose adjustment. The other would be to incorporate it as part of drug development so that they are

studied in the phase 3. You comparing as dose 2 as the two schema when you ask the question schema A versus schema B.

DR. COLLINS: So we always want to be better at getting the right starting dose. The question is how good are we right now? So given the ways that it's done in practice, are we harvesting those data to answer that kind of question?

DR. MADABUSHI: It's a tough one to answer because historically we have done it in one way. We are very good at going about the understanding what is the factor that results in these exposure exclusions and how to go about it. So we are very good at trying to match the exposures on an average. That's what we are good at.

Is it really translating into something that we can evaluate whether it's doing its job or not? I think we do not have that kind of information.

DR. ZINEH: Maybe just to add a little bit on this. It's not going to speak directly to your

question, Jerry, but we recently published an analysis of FDA-approved drugs that use titration as a strategy. A couple of observations: one is the majority of drugs that we approve are not titrated and many of them are not amenable to titration. So the starting dose is the dose, and that's it.

So we don't have any data on how well that translates in the real world other than whatever is anecdotal or whatever is being looked at now with real-world data to say what's essentially the effectiveness of these things in the clinic. But interestingly, of the ones that are amenable to titration, not a lot of them actually use a titration design in drug development.

So it's a little bit of an ancillary topic. But if that's true, if we have diseases out there that are amenable to titration because you're titrating to some biochemistry or some symptomatic effect and it's not being studied that way, you can make an argument that there's probably room for improvement there.

Jay, go ahead.

DR. HUANG: Just to follow up, I think oftentimes, the renal impairment dosing recommendation is not the only one. It's one important one, but there are many other aspects. How do you adjust the dose for hepatic impairment with concomitant medication? Sometimes we don't have the information at the time of approval, and there could be postmarketing commitment, postmarketing requirement, and other unsolicited studies that we have observed.

So we do have experience where we modify the labeling based on what we know, either as PMR, PMC, or publications. We do use, right now we can call, real-world data or real-world evidence for adjustment. I think renal impairment is one of the many examples that we do continue to improve our labeling and to give better information for practitioners.

DR. COOK: I tried to do some homework before the meeting because the shifted exposure-response curves are of keen interest to

me. I did find some -- especially when the site of action is on the tubule side, it has to be excreted, but there wasn't a lot of information.

Why I think that's important is getting things into phase 3 studies, I think we're actually pretty good at predicting doses to exposure match in renal failure, and we can be better and we can make it more rigorous and methodical to know exactly what we are. But if we can't exposure match, it's not the late-stage trial that looks at exposure-response, it's the phase studies. And if you think it's going to be different in those trials, that's about the time you ought to be studying renal impairment that is shifted.

I'll just add that out as we consider things. When do we get the information that that may be different and we may need to do that? Because if you do it in phase 3, that just complicates life more. I'd like to have a situation where we got it right, that we could actually figure out how to use that information to be part of the overall approval package and not

something that stands alone. Maybe you'd have to consider them differently because of safety, because they just have a different safety profile because of the disease.

That to me is the optimal situation. That complexity that I hope goes away that becomes very simple is how do you tell when it's not going to be what I call the norm? But that's my bias.

DR. MADABUSHI: Yes --

DR. COOK: And that was more of a comment. You don't have to respond.

DR. ZINEH: Yes. I reminded Raj that wasn't a question. No, I think this will be good for discussion after we hear the next presentation after the break.

DR. DOWLING: I had a clarifying question regarding the final dose adjustment table that's published in the label based on the different creatinine clearance ranges. Is that based on the point estimate of the clearances of each of those categories, and then is that using generally just the Tozer approach of either changing the interval

or changing the dose based on the adjustment factor?

What's the thought of the FDA on how that actually gets approved? Is that based on a point estimate of clearance?

DR. MADABUSHI: More often than not, because these are excluded from your late-phase trials. You call it phase 2, phase 3, or any other ongoing trials. That's where most often the source comes. But it's not always done in a vacuum. It is informed by some degree of clinical experience where available and what kind of uncertainties might be there. But if you're asking is it like the point estimate kind of thing, generally that's what it is, but there is no one way of doing it. That's why we brought it up, that there are several ways of doing it.

DR. SLATTUM: This is Patty Slattum from Virginia Commonwealth University. I had one clarifying question about this notion of the similarity of exposure-response relationships, and I'm trying to understand if that assumption is

generally true, most of the time true, we don't know. How often do we actually know whether that assumption is real or realistic, and where does that information actually come from?

DR. MADABUSHI: That's one of the challenges to actually have information that will inform us whether that assumption will be true or not. In those very few handful of situations where the expectation was that it could be different was that there was, a priori, a mechanistic basis.

Like Dr. Cook pointed out the site of action is somewhere in the renal tubules or somehow there is an interaction between chronic kidney disease and the indication of interest, which happens in cardiovascular areas, things of that nature. But more often than not, we just don't have the information across the entire spectrum because these patients are often excluded, and we have no clinical experience to say this is more often true or not true. That's the conundrum. We just don't have that information.

DR. SLUD: Eric Slud, University of

Maryland. You've presented very clearly the response curve could change as a function of degree of renal lack of function. Similarly, the safety profile could less explicitly, but in response to the questions, you mentioned that the profile of variability of each of those random variables, there could be a schedule of change, of dependence on lack of renal function.

There are decisions to make based on all of those different possible changes based on what seems to me inevitably are going to be a very small sample of severely impaired, and therefore, there must be some other kinds of prior information you're bringing in, in a systematic way, in order to compensate for that.

Could you comment on that?

DR. MADABUSHI: Sure. There is the challenge that even if information was collected, the numbers could be small enough; that's true. Most of the additions are taking into account the totality of information. We would look at mechanistic aspects. We would look at whatever

clinical experience would be available, and use all of that to translate as opposed to having this a priori assumption, which cannot be tested, but we somehow have to believe that to be true. Otherwise, there would be a gap in the labeling, and there would be patients who might need dosing, and there will be an uncertainty that could exist with it.

So you're right, but we would use the totality of information, and I think the clinical experience would be a lot more helpful.

DR. SLUD: So it seems that whatever you do, there are these simultaneous decisions to be made from a very small final patient sample of extremely impaired. Are you not in a situation of doing extreme extrapolation from a very small number of data points in many of your trials?

DR. ZINEH: This is the secret that no one wants to talk about. The problem with clinical PK studies is that the trade-off is we're taking reductionistic approaches to get a clean answer. You have a better defined population. You have

clearer differentiation between patients in terms of impact on PK. But then you have to translate that to a broader patient context. This is actually not true of just renal impairment; hepatic is the same story, food effect, drug interactions, you name it.

That paradigm though is well worn. And as Raj mentioned, when we say the clinical experience, it's largely hinging on what we know about the exposure-response relationship in the studied population, whether it's phase 2, phase 3. Yes, then you're making very -- we have that implicit assumption that what we're going to say about that relationship in the study population holds true for the extrapolated population.

Our question to you is, is that a reasonable starting point? Should we be assuming that these relationships are the same until there's a reason not to or should we be going into it with a lot more skepticism?

DR. TERZIC: This has been a very exciting discussion, so I will not ask any questions. I

will invite you more for a break. We'll take a 20-minute break and reconvene around 10 to 11. Thank you.

(Whereupon, at 10:29 a.m., a recess was taken.)

DR. TERZIC: We will continue at this point this session. Occasionally we have the opportunity to hear even a broader view on the topic, and this time we have a recognized guest speaker. We ask Dr. Graham to share with us his experiences.

Presentation - Richard Graham

DR. GRAHAM: Thank you.

Good morning. I'd like to thank the FDA office of Clinical Pharmacology for inviting me to present today on industry perspectives on approaches to evaluate the effect of renal impairment on drug exposure. My name is Richard Graham, and I head clinical and translational pharmacology at Theravance Biopharma.

These are my disclaimers. First, from the International Consortium for Innovation and Quality and Pharmaceutical Development. The presentation

presents current perspectives from industry, but it's not meant to represent a consensus view of the full IQ membership or industry in general.

IQ has established working groups on organ impairment and physiologically based pharmacokinetics, and is working to build further understanding and consensus on many of the topics that will be discussed today. From my employer, Theravance Biopharma, the views and opinions expressed are solely those of my own and do not represent those of my current or previous employers.

Today, I'm going to tell you about current practice within the drug industry to assess the impact of renal impairment on the exposure of low molecular weight drugs. There are several challenges with the current practice as you've heard from the FDA speakers today.

From an industry perspective, one of those challenges is the expectation to assess pharmacokinetics in patients with end-stage renal disease. The other challenge, as you've heard

today, is enrolling subjects with renal impairment until late-stage clinical trials. I'll go into each of those in some more detail.

I'm also going to talk to you about some alternate approaches to conducting a dedicated renal impairment PK study: modeling and simulation approaches; totality of evidence approach. This is an integration of translational data that Dr. Madabushi pointed toward. And finally, enrolling subjects with renal impairment in the late-stage trials. I'm going to talk about four potential scenarios as to how we might accomplish that. Finally, I'll end with some additional considerations that are relevant to optimizing dosing instructions for patients with renal impairment.

To assess the impact of renal impairment on pharmacokinetics, sponsors aim to inform labeling for renal impairment with a combination of dedicated PK studies and data from subjects enrolled into phase 2 and phase 3 trials. However, the current practice results in exclusion of

subjects with renal impairment until late-stage trials, which contributes to gaps in the labeling, especially in the extremes, the severe renal impairment subjects.

There are several challenges with the current practice, including current guidance, which suggests that a dedicated PK study in subjects with end-stage renal disease is required, or recommended I should say. There's a limited population of these subjects with ESRD.

It's challenging to complete the studies and there is a potential safety risk to including a new molecular entity that has not yet been approved in this population. In the next slide, I'll talk about how confusion exists within the industry regarding the regulatory expectations to conduct such studies in the ESRD patients.

There's an underutilization of available safety, efficacy, and pharmacokinetic data that can translate into dosing instructions for subjects with renal impairment, and I'll illustrate this point with an example of a drug that was approved

without a dedicated renal impairment PK study. However, the dosing recommendations for subjects with renal impairment are very clear.

The key challenges of the current practice limit enrollment of subjects with renal impairment in late-stage trials. You've already heard a lot about this, but I wanted to spend a minute here talking about a chicken and egg problem, which is regulatory agencies and institutional review boards may have concerns over ensuring adequate safety measures for enrolling moderate and severe renal impairment subjects in the late-stage trials.

The other side of that is that sponsors are also conservative about enrolling subjects with moderate or severe renal impairment into clinical trials because of the risk of contaminating the safety or efficacy results for the primary analysis. So because of these current situations and current practice, we end up with very few subjects with renal impairment in our phase 2 and phase 3 population.

Just one slide on the dedicated PK study in

the ESRD patients. I appreciate the comment that Dr. Sahre made that the FDA's current thinking within the Office of Clinical Pharmacology is that these studies may not be needed, but I want to point out that this is confusing within the industry.

ESRD patients experience significant mortality and morbidity and reduced quality of life. There are less than 200,000 ESRD patients that are not on dialysis in the U.S., and only a fraction of these might even participate in a study. Of those ESRD patients that choose to participate, only a fraction of those would even qualify given the medical history, complications of the disease, concomitant medications and/or their screening criteria.

Dosing these patients with an non-approved drug, again, worst-case scenario for these subjects could be considered a safety risk. And it wasn't until I was preparing for this presentation that I even realized that in March of 2010, there was an advisory committee meeting with FDA where the

majority of the advisors felt that it was not feasible or necessary to recruit ESRD subjects not yet on dialysis to represent the worst-case scenario.

So even though the current thinking within FDA may be that this study's not required, I can tell you that myself and many of my colleagues are confused because the guidance still recommends to do this. So I'm hopeful that we, starting with the conversation today, can move toward a situation where alternative approaches are considered.

In the next three slides, I'm going to level set and describe what is considered to be current state of the art with regards to modeling and simulation for renal impairment.

There are two approaches that are typically used to assess the impact of renal impairment on pharmacokinetics. One is a population PK approach, the top-down approach. The other is a mechanistic PBPK approach, which is considered to be middle out, bottoms-up approach. These two approaches will be discussed in more detail in the

subsequent slides.

Population pharmacokinetics is widely used in drug development, and with regard to renal impairment, it has been used to support enrollment, providing rationale for inclusion/exclusion criteria of subjects with mild, moderate, severe renal impairment in later stage studies. It's been used for study design, including the rationale for selecting doses in subjects in renal impairment in a given study.

Finally, it's often used in labeling. In the pharmacokinetics section of the label, you can see wording like the example provided here, which talks about the results from the population PK analysis and the impact of renal impairment on drug X in the label.

The utility of PBPK approaches to predict exposure in renal impairment is evolving, and the work shown on this slide is from an IQ initiative that was led by Tycho Heimbach from Novartis. In this work, renal impairment data for compounds that are predominantly eliminated by the liver had

validated PBPK models along with data from dedicated renal impairment studies, and these results were collected from 17 different drug companies and represented 18 compounds.

The top line results are that the effects of renal impairment for drugs that are cleared by non-renal routes are modest. The maximum observed mean in AUC was 1.7, 2.2, and 2.2-fold for mild, moderate, and severe renal impairment, respectively; so not large changes.

The vast majority of the predictions were within 2-fold of the clinical observations, and about half of the predictions were even within bioequivalence limits, suggesting that the model is doing a very good job of predicting the impact of renal impairment on PK; again, even for drugs that are not renally cleared.

So the take-away here and the current state with regard to PBPK modeling is that for compounds that have a wide safety margin, PBPK modeling may be used to predict the effects of renal impairment.

In the next few slides, I'm going to go

through what we're calling the totality of evidence approach with regard to evaluating the effect of renal impairment on drug exposure. What the totality of evidence approach is, is an integration of data to inform dosing for subjects with renal impairment.

If we only consider the obvious information, results from mass balance, renal impairment PK study if it's done, and popPK, then there's an underutilization of available safety, efficacy, and PK data that can be useful for dosing instructions in patients with renal impairment.

On the left-hand side, there's a lot of information that can be utilized from the intended patient population, and on the right-hand side, there's a lot of information that can be utilized from preclinical experiments and dedicated clinical pharmacology experiments. In the next slide, I'll walk you through a real example.

In 2012, Erivedge was approved for the treatment of locally advanced and metastatic basal cell carcinoma. Full disclosure, I happened to be

the clinical pharmacology lead on this project when I was employed by Genentech. Importantly, the drug was shown to have a wide therapeutic index, and within the indication, there was a small number of patients that had locally advanced or metastatic BCC and severe renal impairment.

If we start with the panel on the top left, results of a human mass balance study showed that the drug is cleared by metabolism by the liver and small intestine, so it's not predominantly renally cleared.

Before I go into the next panel of data, I just want to provide some context here with regard to the comment that was made earlier. Even for drugs that are non-renally cleared, circulating uremic toxins can have an impact on the pharmacokinetics of the drug and renal impairment. So uremic toxins are known to inhibit drug metabolizing enzymes and transporters, albeit with relatively low potency compared to other inhibitors. With that context, let's move on to the middle panel.

There was a dedicated hepatic impairment study conducted with vismodegib. What you can see on the X-axis is that mild, moderate, or severe hepatic impairment did not impact the exposure of vismodegib in plasma, shown on the Y-axis. Think about what I just mentioned with regard to uremic toxins.

In hepatic impairment, the expression and function of drug metabolizing enzymes and transporters is decreased. Therefore, this mimics what would be expected due to the effect of uremic toxins in renal impairment. So I'm trying to make the point that the results from an hepatic impairment study can be used to translate what we might expect with regard to renal impairment.

Moving on to the figure on the right, I'm going to make a similar point with regard to translating data, and this time from a drug-drug interaction study. It was known at the time that when we conducted this study, that the primary pathway for elimination of vismodegib was through metabolism by CYP3A4 and transported by Pgp.

We did a clinical pharmacology drug-drug interaction study using itraconazole, the most potent inhibitor that is used in the clinic for those two pathways. Even with concomitant administration of the most potent inhibitor of the pathway, itraconazole, there was no impact on the plasma pharmacokinetics of vismodegib. So again, using an analogy, back to renal impairment and uremic toxins, if the most potent inhibitor of the pathway doesn't have an impact on the plasma pharmacokinetics of the drug, then we can translate that to say that uremic toxins, which are less potent, would also not have an effect.

Moving to the bottom panel on the figure, this is the result of a population PK analysis. In this case, there were 58 subjects with mild renal impairment; 16 subjects with moderate renal impairment; and one subject with severe renal impairment that were included in the population PK analysis. The results showed that renal function was not a significant covariate for the primary PK parameters of vismodegib. So taken together, the

totality of evidence for this drug indicated that mild, moderate, and probably severe renal impairment does not impact the PK safety or efficacy the drug.

Even without a dedicated renal impairment study, the current U.S. package insert for Erivedge provides clear dosing instructions for patients with renal impairment. It says that no dose adjustment is required in patients with renal impairment and references the clinical pharmacology section of the label.

Section 12.3 of the label says that mild to moderate renal impairment, based on the population PK analysis, had no clinically relevant effects on the systemic exposure of vismodegib. It also says that the impact of severe renal impairment on the PK is unknown. However, I would make the case that based on the totality of evidence that I showed on the previous slide, I think it would be fair to make the leap to say that this is unlikely to be impacted in severe renal impairment as well.

The label is relatively silent with regard

to safety and efficacy in patients with renal impairment. However, again, using a totality of data approach, especially with regard to moderate renal impairment where there were 16 subjects included in the analysis, I think it would be appropriate, at least in my opinion, to evaluate the safety in those subjects and see if it's different or similar to the general population.

So while that represents the good example, I think, I still think there are opportunities.

Now I'm going to transition into describing some potential approaches to evaluate the effect of renal impairment on drug exposure. As far as I know from reviewing the literature, none of these approaches have been published upon. These are just examples that I've mocked up for the consideration of the FDA and the advisory committee.

I'm going to talk first about a sequential approach, where we start with a particular study, analyze the data, move to the next study, analyze the data, and move to the next study. Next, I'll

talk about an adaptive design where you're making adjustments by looking at the data in subjects with renal impairment during a trial and making adjustments accordingly. Another potential scenario could be doing a renal impairment substudy -- sometimes this is done for QT studies -- and then finally an open-label extension idea.

Before I do that, though, I just wanted to set the stage with some key highlights from a poster that was presented in 2014 by Islam Younis. In this poster, Islam noted that only 4 percent of FDA-approved new molecular entities from 2000 to 2012 require dose adjustments in subjects with mild renal impairment. The take home from this work was that subjects with renal impairment should be enrolled into late-stage studies using a risk based approach, and that approach should be based upon data that comes from the preclinical setting, as well as early clinical data.

So it might seem intuitive to people here that you would take this sort of approach, but I

can you having worked at multiple drug companies over the years, this is always a conversation within the project team. Whenever you're moving into late stage, like I said earlier, it's a consideration of potentially contaminating the safety database. So even conversations around enrolling mild subjects is something that happens routinely.

In this slide, I'm showing an example of a sequential approach to enroll subjects with renal impairment into late-stage studies. If you look at the boxes on the top of the slide, you start with a phase 2a study, placebo and three active dose groups. The next study would be a phase 2b study, placebo and the same three active dose groups, moving into a phase 3 study with only one active dose group.

Using the risk assessment based upon preclinical and early clinical data, you could decide to enroll mild or mild and moderate subjects into the first phase 2a study. So in this case, let's say we enrolled mild subjects. At the end of

that study, we look at the pharmacokinetic data, and if the exposure is not apparently different than subjects without renal impairment, in this case less than 2-fold, one could make the decision to enroll moderate renal impairment subjects into the next trial; again, randomized to placebo in all three active doses.

At the end of that study, you could evaluate the data. Again, if the exposure looks similar and you could use some cutoff of, say, less than 2-fold and the tolerability is good, then one might make the decision to enroll mild, moderate, and severe renal impairment subjects into phase 3.

If you follow the bottom path in the decision tree, at the end of that initial phase 2a study, there's an observation that exposure is different. You could decide then in that case to exclude the high dose and enroll subjects with renal impairment at either of the low dose or the low dose and the mid dose.

At the end of that study, again, if exposure is changing and if there's a safety

concern, then you may decide not to continue enrolling towards severe patients and do a risk assessment on whether or not moderate patients should be enrolled.

The next example would be an adaptive design, so as opposed to doing this in sequence, now in a phase 2 safety and efficacy study, you could enroll mild and moderate subjects using this risk-based approach. A population PK model would be established based upon early clinical results -- this could be based on phase 1 results, for example -- and the sponsor would predefine a 90 percent confidence range for the plasma concentrations; what's expected in that general population.

After enrolling 6 to 10 subjects, for example, you could look at the pharmacokinetic data in that ongoing trial, and if the exposure is within the predefined range, as shown in the top right, then a decision can be made to ungate or enroll subjects with moderate or severe renal impairment, and ideally, this would be written into

the protocol and an adaptive design, so it doesn't require a protocol amendment.

In the other situation where the exposure is not within the predefined range, a decision could be made to enroll subjects with renal impairment at a reduced dose, depending on the magnitude of that change, or the sponsor may decide at that point to go ahead and conduct a dedicated full renal impairment study to better understand the impact.

The third example that I'm going to talk about is assessing renal impairment within a substudy. This is a substudy of your main phase 2 or phase 3 safety or efficacy study. This could be done at a select number of centers within your, probably, global phase 2 or phase 3 trial.

This would provide the opportunity to assess renal impairment without complicating the analysis of the main trial. This is often a concern, as I mentioned earlier; so substudy, so the results could be treated separately. This would allow for dose adjustments within that

substudy in subjects with renal impairment, and you could have an option if the results at the end of the study look to be similar between renal impairment and non-renal impairment to combine the results, which may increase the sample size of your main analysis, or if the results are different, then you could keep those two studies separate. But in either case, having this renal impairment substudy informs labeling in that population.

The last example that I'll talk about is renal impairment in an open-label extension study. In this case, you have your main phase 2 or phase 3 efficacy study, in which case you may be enrolling only mild patients, given the situation that we talked about earlier. At the end of that study, patients can roll over into an open-label treatment extension.

Again, these would be mild subjects only. This allows for an opportunity to assess renal impairment, again, without complicating the analysis of the main trial, but it would most likely require a de novo cohort into this

open-label treatment extension, again, because you're only rolling over subjects with mild renal impairment. For this de novo cohort, additional visits for safety and PK assessments should be considered.

As I said at the start of the presentation of those four scenarios, I'm not aware of any real examples where those scenarios have been used to inform renal impairment, and that's probably because there are a number of complicating factors to consider, and I've listed some of those here.

The examples provided may be an over-simplification. For example, it's not that often that we go from phase 2a to phase 2b with the same number of doses and the exact same doses. Sample size of early proof-of-concept studies might not allow for enrollment of enough subjects for decision making.

There can be organizational complexity with analyzing safety and even PK data from blinded, ongoing, late-stage trials. There can be operational complexity, especially for the adaptive

approach of getting the data from the bioanalytical lab in real time to be able to do that PK assessment.

There's concerns with the potential for contamination of the safety and efficacy analysis population in any of those approaches that I mentioned. Institutional review boards or investigators may not be comfortable with a modeling approach to ungate enrollment.

One of the things that I think we should all keep in mind as well -- and I'm happy that we're here talking about this topic today with the FDA -- sponsors generally conduct trials in a global setting. So it's not just the FDA's feedback that we need to think about but it's also what our global health authorities are going to think of this approach.

A point that was mentioned in one of the FDA presentations is that renal function may not be stationary over time. In these non-single-dose studies where we're enrolling renal impairment patients into late-stage trials, over a period of

time, renal function may change, which can lead to under or overdosing. So that's an important point that we need to be considered. There are a number of obstacles with any or all of these approaches that I've outlined, but I don't see any of these that are insurmountable.

Some additional considerations to factor in with regard to providing optimal dosing dosing instructions in patients with renal impairment, similar approaches to the totality of evidence approach should be considered for small proteins, antibody drug conjugates, and relevant complex molecules.

Special consideration should be thought about for organ restricted or organ selective drugs that have low systemic exposure and wide therapeutic index. It's highly unlikely that renal impairment is really going to have an impact from a safety perspective on these drugs.

There could be a provision to allow a model-based extrapolation of systemic exposures and extend proportional dosing recommendations from

adult to pediatric subjects with renal impairment; and finally, provision to update the label post-approval using real world evidence regarding the safety of the drug and effectiveness in renal impairment.

In conclusion, clarity as requested regarding regulatory expectations for enrolling ESRD subjects. I think we agree that alternative approaches are needed for collection and integration of safety, efficacy, and PK data that can translate into dosing instructions for patients with renal impairment.

Enrolling subjects with renal impairment into late-stage trials will require multiple stakeholder alignment, first of all, within the industry, clinical pharmacology, biometrics, regulatory, and clinical science. We'll all need to come together and think about how to best take on one of these approaches. I would assume within the FDA the same would apply with OCP and other functions as well.

This is not likely to be a

one-size-fits-all approach. I agree with the comment that Dr. Reynolds made; let's try to make it simple, but it is still relatively complicated, and it may be case by case in terms of which approach makes the most sense. I would suggest that further interaction between FDA and industry could help to lead toward potential alternative approaches to evaluate the effect of renal impairment on drug exposure.

Briefly, I'd just like to acknowledge the IQ organization. This was a bit like drinking out of a fire hose over the past few weeks and pulling all the information together from a number of different companies, but I appreciate all the input. Lee and Sandhya were especially helpful in organizing a number of conversations over the past couple of weeks.

Other colleagues at Theravance contributed to my presentation as well. Jin and Tong Lu from Genentech; input from my collaborators at Celerion; and from my mentor Karin Jorga from KarinJorga Life Sciences consulting. Thank you.

Clarifying Questions to Presenters

DR. TERZIC: Thank you very much. This was a very clear, I think, presentation that provides the committee and the FDA more generally an opportunity to reflect, and I'm very grateful to you for making that effort. One aspect that you also brought that was not brought up earlier is that while we focus on small molecules, which specific traditional dose-response curves that define the direction and safety, we have to be obviously aware of the broadening of the portfolio or therapeutic armamentarium that includes increasingly biotherapeutics that you mentioned.

So I think it's important that we keep this in mind, and maybe that's an opportunity for this center to also work with other centers within the FDA on the broader subject.

At this point, I will open the opportunity for the panel members to ask some clarifying questions. Maybe we can have our speaker actually come back, if you don't mind, to the podium, or at least use one of those microphones. Yes, that

would be great. And we can get started.

Shiew-Mei?

DR. HUANG: Thank you for the very thoughtful presentation. I think your points are well taken about the ESRD. We did discuss at 2010, as you and Dr. Zahre mentioned -- the advisory panel did indicate that that is not the population that will be suitable for us to pursue as the worst-case scenario. That's what we were proposing to do 10 years ago.

Since then, we have presented at public meetings papers indicating perhaps the severe renal group will be the worst case that we could predict, especially for drugs that aren't metabolized. Or for drugs that were not clear about the extent of renal clearance, then that could be a reduced design.

So I guess we'll somehow improve our communication because the ESRD patient, the only one of the issues for that guidance, and it took us a while. It has taken us a while to get the revision, which should be out.

I think the other good point that you make is to use all the available data. I think you have shown us a slide where we may have only used one or two -- powerful information. I think that's in slide 9 or 10. I think that's a very good point. I believe we really need to know our disposition well in order for us to make -- okay, this is slide 10.

There is many other information that you mentioned from drug-drug interaction and hepatic impairment. We can get inference about how renal impairment could affect not just drugs that are metabolized, not renally cleared but also for renal-impaired drugs as well. Not only will GFR be effected. Some of the renal transporters can also be affected in addition to the decline of GFR in renally cleared drugs. So that's an excellent point.

I do have a clarifying question on number 9. That's the IQC study. Obviously, we want to use all the information in order to make a conclusion of whether PBPK has predicted well on

how renal impairment affects the PK. Your fraction of renal elimination here is 1 to 45 percent.

If the 45 percent is the absolute number, I wonder how many drugs are above 30 to 45 renally cleared, and whether we know the non-renal pathway. We want to use all the information, [indiscernible] CYP2D6, OATP2B1, or others that we may have considered that renal impairment can affect their effect, because if we have many drugs that are metabolized by certain CYPs, we consider it not to be affected by the circulating toxin. Then obviously, you would have the results right inside the boundary.

I think especially, you mentioned 0.8 to 1.25 or within 2-fold of the clinical observation. I think that will -- I look forward to your paper, but I was curious about do you have all that information.

DR. GRAHAM: Thanks for the clarifying question. This slide was meant to be a high-level overview of the work that was done. I don't have an answer to your question about which proportion

of the drugs had a higher fraction of renal elimination, but that will be forthcoming in a publication; good question, though.

DR. AWNI: Walid Awni. On that PBPK, where are we at scientifically? Is it really a fantastic approach in new predicting or are we limitation? We are moving in the right direction, but in your assessment, feeling, gut feeling, how far are we? Because this could provide significant advantage to us very early on about predicting.

So where do you see it? Where do you see the science going in that particular area?

DR. GRAHAM: First of all, I'm not a modeler, so I'll do my best. But at least with regard to the thinking within the IQ working group, this is certainly evolving, and the work that was described here, as I mentioned, will be published soon, and I think it's a good start. The idea would be to get to a point like we are with drug-drug interactions to be able to have so much confidence in what's included underneath that model, that we have a good idea of what the

predictions are going to be relative to the observations.

I don't think we're there yet, and I think the general thinking is that we can utilize PBPK perhaps for enrollment decisions with regard to clinical trials, perhaps with some of the scenarios that I outlined, but we're probably not there yet with regard to labeling. That's at least my opinion.

DR. NOLIN: Tom Nolin from Pittsburgh. I have a couple of comments. The first is related to what Shiew-Mei raised with respect to the GFR cutoffs, going as high as 45 percent, for example, in slide 9. But I would follow that up by simply saying that it's important to recognize, in our considerations going forward, that the impact of kidney disease, or renal impairment, on non-renal clearance is differentially affected.

To the extent that we can identify drugs as substrates of specific pathways, I think that we can make better -- we would be better informed with respect to whether or not they might be impacted.

We have some data coming out that has clearly shown that there are differential effects. I think it's not ideal to sort of lump these all as simply non-renally cleared drugs because there clearly is an impact, a differential effect.

The second point, again, just a comment, relates to vismodegib and this strategy that you used, using hepatic impairment, as essentially a surrogate of uremic toxins, and extrapolating that data to suggest that renal impairment and progressive renal impairment doesn't affect the pharmacokinetics.

I think that's flawed because it assumes, number one, that the only mechanism of altered non-renal clearance is through some acute inhibitory process, for example, that may or may not be reversible or maybe it's competitive or not, and that's clearly not the case. There has been some data suggesting that expression has also changed, and that it's not simply uremic toxin effect.

The other is that it fails to consider the

other physiological effects of kidney disease upon pharmacokinetics, and thereby impacting exposure. So the conclusions that were made in this, in my mind, are somewhat limited because to suggest that this model -- which assumes that hepatic impairment mimics the physiological changes of renal impairment, and therefore we can say there's no change in exposure, in my mind are not accurate.

I'd be interested in hearing what some of our nephrologist colleagues would say about that. But clearly, the physiology associated with progressive kidney disease is much different in situations. Particularly, well-dialyzed ESRD patients, for example, is much, much different from non-dialyzed severe renal impairment, which is much different from hepatic impairment.

DR. GRAHAM: Maybe if I could just respond to that last point. That makes good sense. I just wanted to make the point, though, that this is a totality of data approach. So the hepatic impairment, I agree, on its own would not suffice, but when you add everything together, I think it's

one piece of the puzzle.

DR. SUN: I have a clarifying question. Can I also refer earlier -- we can't ask FDA folks to help my question. For example, slide number 9, really then, the survey is based on the renal function, the AUC, or even the earlier presentation, like 2-fold perhaps, even for those drugs.

Has any of your group, or maybe early FDA, evaluate, under different renal function, the clearance -- no, sorry, volume distribution change. Even for those drugs, which are liver cleared, they may not change the clearance, but the volume distribution change, that's what changes the curve and shapes everything. I refer to Dr. Pai's question that will change the concentration.

Do you know with renal function, often patient will have volume distribution change. Do you have those surveys? Even early FDA, do you have those type of data?

DR. GRAHAM: Sorry. Is the question for me or for FDA?

DR. SUN: Both.

(Laughter.)

DR. GRAHAM: I'll defer. I don't have a comment.

(Laughter.)

DR. SAHRE: I don't think that we necessarily have a survey of how the volume changes whereby drug or for specific drugs. We just know that the volume can change for patients with renal impairment, and maybe I'll turn it over to Shiew-Mei.

DR. HUANG: I was just going to say, I guess your question is about the apparent volume of distribution with the oral administration. We did have some calculations, but I don't recall a constant trend that we can say it. Oftentimes, we don't have a lot of information, like protein binding and many important information that we will need but we don't have. That's why, actually, we're looking at the other direction to see if they have theoretical comments.

DR. NACHMAN: As a nephrologist and

non-pharmacologist, I worry that going from CKD3 or mild- moderate chronic kidney disease to severe kidney disease, these kind of effects on perhaps volume of distribution may not be linear. If we think about edema, hypoalbuminemia, concomitant drugs, metabolism, the effect of severe kidney disease on other physiologic effects could affect both the efficacy and the safety of a drug in a nonlinear way with respect to GFR alone.

DR. COLLINS: I'm not really concerned about volume distribution. It doesn't affect the steady-state concentration. It doesn't affect the area under the curve. So whether there is edema or not may have transients, but they shouldn't be too long, and they shouldn't affect the therapeutic index.

DR. SUN: If the drug is AUC driven. If it is Cmax driven, then I think you're right. If the toxicity is Cmax driven, then that may change.

DR. NACHMAN: And edema may not be steady state, especially if we're now talking about patients on dialysis. It can change dramatically

from day to day and from other drugs. Again, I'm not the pharmacologist, so I'm not going to argue. But it's not that the edema is going to be the same on day 1, and day 5, and day 12.

DR. COOK: I would just like to mention in cases where -- Jack Cook, industrial representative. Typically in cases of renal impairment, we'll actually see a decrease in clearance, so you have less of a peak-to-trough fluctuations, depending on how you change the dose. So even if it's Cmax driven, it may not be as a concern because you're tending to flatten the curve.

They're not many drugs that I know -- even though you make a perfectly obvious statement about the state of edema, and not even edema, there are not many drugs that I know of that even in practice that you dose a lot differently depending on the state, unless they're cleared by the dialysis unit or something like that.

I take some comfort -- because I remember the case before -- of course, I'm not that old.

But reading about the cases before pharmacokinetics came into view, there actually were observations that select populations had different profiles, and then they used kinetics to explain that, and that's how we got into all of this trying to match exposure.

So I take some comfort that in my literature search, I didn't see a lot of articles about there being a inherent, harder-to-dose people with renal failure because of some fear of not being able to factor something in.

DR. TERZIC: As you proceed with the questions, I'm going to encourage you to frame them more as clarifying questions to the speakers. That will be helpful.

DR. DOWLING: Richard; a clarifying question. You mentioned a couple of times during your presentation about cases, including renal impairment, wherein your phase 2 and 3 studies could potentially contaminate the safety data.

I'm a little concerned with that type of comment. We obviously want safety data as much as

possible from as many patients as possible. But in the case of renal impairment, if you're exposure matching and renal dosing to a point where AUCs are comparable in your renal impairment, wouldn't that somewhat adjust in terms of -- again, exposure would be similar, and then in that case, you are measuring safety on a level playing field there; maybe clarify that, the issue of contamination.

DR. GRAHAM: Sure. Absolutely. To be clear, I'm all for the approaches that I outlined and moving toward a better future where we're collecting these data, but it is a real situation. And whether you use the word "contamination" or something else, when sponsors are designing late-stage studies, they want to have the cleanest safety and efficacy population as it relates to the intended population to be treated. Including patients with other comorbidities, whether it's renal, hepatic, or something else, it's something that could potentially confound those results.

So I'm not saying that it makes the best sense, but I'm saying that it's a real situation

and a real problem.

DR. KRAFT: Richard, I want to thank you for putting out, in sort of a blue sky, the potential for late-stage proposals. Would you envision that changing the early stage paradigm of a reduced or a full approach prior to this, or would that keep that framework in place?

DR. GRAHAM: I think it would depend. I think the more you know about the molecule in early development, the better to inform what you might do, especially with regard to the risk-based approach and enrolling those subjects.

In my opinion, that doesn't necessarily need to be a dedicated single-dose PK study, though. That could be other things like taking data from your first in-human and looking at the impact of creatinine clearance, for example, there, using preclinical data, really understanding as much about the pathways of clearance as you can early on, ideally, in lieu of a dedicated renal impairment study.

DR. COOK: This is a clarification comment,

not a question. I just want to make sure the panel understands what we mean by contamination in that in a label, any adverse event that appears above a certain level gets put in, whether it's on placebo group or the patients being treated.

If you have a sicker population coming in, they will have adverse events associated with a disease. So the idea is when you list all of those, there will be some that look worse from the drug that happened by not due to the drug but happened by happenstance. So the fear is that you get saddled with that, and then maybe a competitor is lucky and they don't get saddled with that.

I'm not saying that's right, but I want to explain that that's kind of the fear of when you include the sicker population, that's what your label may look like. I think there are ways around that. Hopefully, we can come to that, but we'll figure that out as we proceed.

DR. MORRIS: Can I ask -- Ken Morris from Long Island University. It was a great presentation. You covered a lot of the same

concepts that our colleague from FDA presented. For the purpose of our meeting today, are you commenting on whether there should be a paradigm shift, or is everything that you're talking about contained within the questions that we're addressing? And maybe this is a question for FDA.

DR. GRAHAM: Maybe I'll start. I tried to be relatively clear in the presentation. I would say even though I'm not formally here to represent industry, there is a general consensus within industry that we would like to move toward different approaches, alternate approaches.

DR. MORRIS: Thank you.

DR. BERINGER: Paul Beringer, USC. I just have a question about your substudy concept. How is that going to improve the efficiency versus a stand-alone study in patients with renal disease? Are you talking about a full or a partial design? How would that work?

DR. GRAHAM: Are you asking about improving efficiency relative to the current dedicated PK studies?

DR. BERINGER: Correct.

DR. GRAHAM: It would be less efficient. It would probably be more costly. But I think it would provide more valuable information, at least in the intended patient population. You would have more patients, you would have the ability to dose-reduce within that study, and you would be dosing more than single dose. So you might be able to get some important safety and efficacy data as well.

DR. BERINGER: But you still propose to have varying degrees of renal function or is it going to be just partial, mild, or how would that work?

DR. GRAHAM: Again, using a risk-based approach, I would assume that we would want to enroll especially patients with moderate renal impairment and possibly severe. The idea is to get as much of that information to provide dosing instructions of those patients as we can. I think that's consistent with what FDA presented as well.

DR. ZINEH: Just seeking clarification on

your last comment about industry wanting to -- and I understand the caveat of you're not speaking for everyone, but there's an interest to move in other directions.

Is that because of perceived limitations or ambiguities around the current reductionistic approach, or is it because you see more value in the information coming out of these alternatives, or both?

DR. GRAHAM: No. Thanks for asking. It's actually the latter. It was really clear in the discussions with IQ that we can conduct the dedicated renal impairment study. I mentioned the issues with ESRD, but it's easy to do a study in mild, moderate, and severe renal impairment subjects. In general, though, we feel that the state of the art is lacking. We could be doing better with regard to informing how to dose these subjects.

I gave the example of the Erivedge label, but there are plenty of other labels that are relatively unclear based on single-dose PK results

and even limited population PK analysis. So there was a lot of enthusiasm within IQ as we worked up these different ideas to move in that direction, really, I think for the right reason, which is to provide better dosing instructions for patients.

DR. TENJARLA: Srini Tenjarla, industry rep. I completely tend to agree, the comment you just made, in terms of moving in a different direction, not because what we have right now is not necessarily working, but some of the options that are presented combined together can actually give a better picture, and I think you did a very good job. I did actually look at the slides earlier as a member the IQ.

DR. TERZIC: Again, a very productive question session. I think at this point, we will take a longer break, a lunch break, roughly an hour, and it will be great if we can reconvene around quarter to 1, and then start shortly after our afternoon session. Thank you.

(Whereupon, at 11:45 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:49 p.m.)

Open Public Hearing

DR. TERZIC: We will be starting the afternoon session, and the first part of the afternoon session is devoted to the open public hearing session, so I will read to you some of the language that the FDA has prepared in that regard.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages the open public hearing speakers -- most likely today, we'll have one speaker -- at the beginning of your statement to advise the committee of any financial relationship that you may have with the sponsor, products, or any other type of relationship you wish to disclose.

This relationship may include, let's say, financial information, including sponsor's payment for travel, lodging, or other type of expenses related to the attendance of this meeting. Likewise, the FDA encourages the public speakers at the beginning of their respective statements to advise the committee if you do not have any financial relationships. It is also recognized that if you choose not to address the issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore,

please, only when recognized by the chairperson, take the opportunity to address the panel, and thank you all for your cooperation in this hearing.

We were expecting that we will have two speakers today. I was just told that speaker number 1, he has apparently not signed up. Let me confirm that that's the case.

It appears to be the case, so we will be moving to speaker number 2, which we'll like to invite formally to the podium. Please introduce yourself. State your name, the organization that you represent for the record of this hearing. Thank you.

DR. CHOU: Thank you. I'm Ting-Chao Chou, born in Taiwan, natural citizen, U.S. citizen in 1976. I received my PhD degree from Yale University and pharmacology training at Johns Hopkins University School of Medicine. I joined Cornell University [indiscernible] professor, and I work mainly at Memorial Sloan Kettering Cancer Center in New York.

I retired from Sloan Kettering in 2013, and

I formed a company called PD Science, LLC, which I have no conflict or any pharmaceutical product. I'm mainly a theoretical pharmacologist.

My topic is the mass-action law based pharmacodynamics theory algorithm for digital biomedical R&D, and for basic drug evaluation general guidance. I'm talking about general. It's not drug specific, not organ specific, and not disease. It's the basic physicochemical principle of mass-action law.

First, I like to introduce the unified pharmacodynamic/biodynamic theory derived from mass-action law. The basic example is the median-effect equation, which indicates fraction for any drug, fraction affected, fraction unaffected ratio equal dose, and the median-effect dose ratio to the M's power.

DM is potency, IC50, LD50, ED50, median-effect dose for the potency, and M is the dynamic order which defines the shape of dose that occurs.

The median-effect equation, as you can see,

everything is ratio. When there's ratio, everything cancels out. It doesn't matter your drug mechanism or your drug unit can be nanomolar, microgram per cc, milligram per kilo, or international unit, or [indiscernible], or multiples of infection, for example.

So it's very broad. The arrangement of the equation gives rise to the Michaelis-Menten equation, and gives rise to Henderson and Hasselbalch equation of pH, and also gives rise to Hill equation, and Scatchard equation.

Retrospectively, it's not [indiscernible] it's not surprising that the DM is half affected, half saturated, or half ionized, or PK, and K for Hill equation, half occupied, or Scatchard equation for receptor half bond and half free.

It's a very general principle. Extension of median-effect equation gives rise to [indiscernible] effect equation. We have a paper published in 1984. Just one article alone received 6,100 citations; 1,200 journals virtually cover entire disciplines of biomedical sciences. In

fact, three years ago, Elsevier recently said [indiscernible] article from 1984 made history.

This morning and here, we talked later of PK and particular emphasis of PD, pharmacodynamic. Here, PB is the fundamental dose and effect mathematical relationship here, and the PK is empirical observation size that has no model. PK is just the intermediary stamp, ADME, within the PD domain. PK is a single resource, and you can study for 1 year, 5 years, and even 10 years, no end of it.

Here I emphasize PD should have higher priority than PK in drug evaluation and regulation. PD can avoid wasting time, effort, and resources. PD can reduce R&D [indiscernible] rate and save money and effort. The biomedical community, in quoting FDA especially, needs to define what is PD; nowhere can it find, actually. It's so important, any drug evaluation, is still talking about PK. PK is just empirical science. There's no model for it. This of course reduces the confusion, insufficiency, and waste of resources.

Here, this table, I compare PD and PK. PD studies what the drug does to the body. PK studies what the body does to the drug. PD studies what it takes to be a good drug. PK helps proper use of a drug. PD has a rigorous [indiscernible] derived equation. PK only has empirical formula, and nothing is really derived. Also, PD studies efficacy and toxicity. PK studies none of them. Then why emphasize PK instead of PD, is my basic question.

A lot of PK at FDA are influenced by Lew Sheiner and Lesko. If you look at the publication, we compare showing entirely PD biodynamic principle with so-called exposure to response analysis or model-based drug development, or drug-drug interaction. Lew Sheiner and Lesko, they actually derive a single equation; it's empirical. They look, and this lack of theoretical basis and no algorithm was non-quantitative.

I believe, I compare two methods in terms of Googled [indiscernible] citation with science [indiscernible] citation, and number of journals

citation. You can compare the PD and so-called PK, and actually never define PD.

A very important PD theory -- median-effect equation, computer simulation, dose and the curve with hyperbolic curve or sigmoidal curve, all can be transformed into a straight line with a different slope. If hyperbolic, [indiscernible], N equals 1. If greater than 1, it's sigmoidal. The greater the value, the greater the sigmoiticity [ph].

Also, for dose-effect curve, there's a different potency. It also can be transformed into a straight line. The potency is referred to as X intercept. It determines both the shape and potency with a single equation and single software.

The 2 data points theory, like this line, there are 6 data points. Any 2 data points define the same straight line. This is simple mathematics. Reverse logic is any 2 data points can simulate the entire dose-effect curve. This totally new idea has never been told before, but in my lab, I've been using that for decades.

Why 2 data points? People say, how is it reliable? The third data point is dose general. The fourth data point is the median-effect dose, which is a reversal reference point and dynamic [indiscernible]. So 2 data points become 4 data points and 3 data points become 5 data points.

This is so important in an in vivo situation. There are too many doses. It can be [indiscernible]. If it's too low, it's ineffective. So you have a limitation in which you can do as many points as you want. But this provides a new avenue with more experimentation with fewer data points and a clinical trial protocol design using fewer points, and of course fewer patients.

When I say point, it's not number of patients. It means the data for 1 dose and 1 point. With 1 point, you can have 5 patients, 10 patients, 100 patients. That's my theory.

So I'm not emphasizing the variability of biological science or diversity. This morning's talk talked about diversity and examples of data

points. I'm talking about how you accurately determine data by how you analyze your data. For example, in vitro, you can do very accurately. In animal, it's of course a little more difficult. But there are still measures available that can be very quantitative, very clear, and a very simple conclusion.

Here is a comparison of 2-drug combination using my PD theory. It's called Econo-Green, small-sized experimentation. I compare in vitro, in animal, and in clinical trials in terms of time and cost. Time can be weeks, months, or over one year, and the cost can be a few hundred dollars to several thousand dollars in animal, or $10,000 in clinical trial, or millions, and even hundred millions.

The theory applies to in vitro, in animal, and in humans, the same definition, the same equation, the same [indiscernible]. This can streamline the regulatory basic guidance. The theory I presented today actually has been presented in Switzerland and in Bonn, Germany.

Four weeks ago, I presented all these data, more than this, at the Johns Hopkins University School of Medicine.

So I present here, just that you know, a very simple, easy way to streamline. If you keep tracing the trivial and every variability, there's no end of it. For example, in terms of a 2-drug combination, it's very easy in vitro. I can do it in 2 to 3 weeks. In animal, I can do it in 2 to 3 months. In clinical trial -- I'm not a clinician, I'm a PhD -- it can be done. I have a proposal actually presented at Johns Hopkins University and other places, in Asia, too. So it is so simple and fully automated.

In terms of drug combination, I think it's very important because in cancer therapy, AIDS therapy, there's always a multiple drug. In traditional Chinese medicine, there's always a multiple drug. So drug combination is everywhere, even if they approve many drug combinations.

The first requirement of the definition is what is synergy? The DBI, they never mention about

what is synergy. Synergy is so important because it's everywhere. Here, this is 10 plus 120 years -- 10 synergy if determination. Look at it entirely, and my article, 4,800 citations. This is the trend over the past 5 years. Look at other methods. Many studies teach, and they miss the point.

Drug combination --

DR. TERZIC: At this point, I'm sorry, but we'll have to --

DR. CHOU: Okay. There's no end of my presentation, so I stop here. I have a few more slides, which is very important, but you can -- [mic off].

Questions to Committee and Discussion

DR. TERZIC: Thank you very much for your time and for appearing in front of this committee in the open public hearing. This portion of the meeting is now concluded. We will no longer receive any comments from the audience as we proceed and bring our attention back to address the task at hand.

We will need now to carefully consider the data that has been presented this morning and start formulating our advice to the committee. So typically, what we do in this setting, there will be a reformulation of the questions. I will read them out loud for the committee, and then we'll proceed, working closely with the FDA colleagues to bring some consensus. I think the keyword here is "consensus," and if you can help me formulate the most salient point of the consensus, I will write them down on our behalf and read them to you before they're entered into, actually, the final language.

Please, if we can hear the first question that we have to address here. Today, the first question, just to remind you, is to offer our opinion, essentially discuss what alternative drug development paradigms would encourage the inclusion of patient with certain degrees of renal impairment in late-stage clinical trials without the need of a stand-alone renal impairment study?

The advantage and disadvantages of these proposed paradigms will be also useful to discuss.

So again, the focus is how to enhance the inclusion of patients regardless of their degree of renal impairment, is most critical question for the day.

Who is willing to get this started? We can adjust the wording of the question as well, as we keep on discussing. So keep that in mind. We can do it right away or this can evolve as part of the discussion. If some words are superfluous, it's always nice to have them shorter, but if you feel that we need some additional explanation, we can do that as well.

Why don't we start at the very end there?

DR. AWNI: I was going to just jump and start. I think it's a fantastic opportunity if we actually think through how should we do the renal impairment, what information and how we're doing it right now, what study, and what paradigm.

I think we're kind of faced with lacking some information because these are very small. We're talking about mild to moderate, but really severe to end-stage renal disease because it looks like 75 percent of the label have some information

on mild to moderate and others; so how do we get more involvement of a patient and how to advance it without just doing a single study?

It is a tough topic because these patients, there are a very small number of them, and we are trying to assess the impact of the renal impairment. But then you have an oncology drug that also could be, should you do the study, a renal impaired cancer patient to also look at benefits, so it becomes more complicated.

Personally, I believe we need to have more information, more actually to encourage, and the FDA has done a fantastic job in company and others, to say come to us with your argument why you should or why you shouldn't, but make an argument. We're not going to include renal impairment because. What is that because, what is the argument for and against, and then build on such information about how people approach it.

The other piece of it, I do believe that -- and I think Richard Graham talked about it -- we don't use as much information from the

phase 2 and phase 3. Often sometimes we'll face that the data that we collect -- although the experiment is done, but the data that ends up in the database is not clean enough for us to actually make a determination related to the renal impairment.

The measure of creatinine is taken as a safety measure. It's in the local site. It doesn't end up in the central study. So how can we do a better job with the information that we currently spend money to do and collecting it so we could make a determination.

I am a very strong supporter of totality of evidence, and I tend to feel that we don't have enough information to say do this or do that at this time, but we need to encourage a broader gathering of information and encourage that this is okay to do. This is okay to actually include, but make an argument, and make it so that IRB could believe it, the upper management in your own company, and the FDA.

Also somebody said we do it for global

audience. Other agencies also have an impact on how clinical trials are done. So personally, I believe we need to actually advance it by encouraging further experimentation in this area.

DR. COOK: I think there are a couple of prerequisites before one decides whether they can include it in a trial. One is am I going to accurately pick the right dose for these individuals based on the information I have so far? I think we're there, but what we haven't done is a good job of quantitating how well we predict and how well we need to predict.

So I think some thought should be given to that, and by that I mean methodology, being rigorous with that, basing it on a bunch of drugs that we already know things about in order to see what we think the odds are for the next drug.

The other one was the one Raj brought up, is do we think that the exposure-response is going to be the same in this population or not. My bias right now is we may be able to default to it's going to be the same, but it comes at a caveat. I

don't have a lot of data to present that. I only have the lack of data when I go out and try to look for other cases where something like that has occurred.

Then it comes to operationally how to do it. Let's say we include them in the trials. There have been occasions where I propose something like this, and I've had a little pushback from the agency when I wanted to include patients with an altered dose to be analyzed in the exposure they were matched to. It's not the traditional, I'm going to pairwise compare different doses, and they didn't receive that dose that the normal renal function did. Granted, that was a few years ago. I think it may have changed in the agency, but remember, it's not just the FDA because we do global trials, and we've got to convince everybody for that.

Finally, there's a caveat where I'm really excited about this. I'm still wondering when we open it up, will we be able to recruit enough patients to tell whether it matters or not into

these trials. Part of me is thinking that we may be able to recruit enough to tell us not hugely different, and that may be okay, but we may not get down to enough to where we're as confident about the precision of that as we are with other groups.

I'll leave it at those because we've got a lot of people who want to talk.

DR. PAI: Amit Pai, University of Michigan. The draft guidance was issued March of 2019 for cancer clinical trial eligibility, for organ dysfunction, and there are specifically 4 bullets that address renal dysfunction, which are really salient and actually address a lot of the things that were discussed today.

I think one of the points that was raised earlier in the presentation was about serum creatinine criteria as probably not being appropriate or thinking about it as just using a GFR based approach for inclusion/exclusion instead of creatinine.

Another is just adequate justification from the sponsor for the rationale of exclusion, why

they're excluding for that specific compound. The third bullet is that of this totality of evidence idea. What is the justification? Is there going to be more risk in that population? If there isn't, then there really isn't a rationale to exclude that population.

The fourth is really the timing of that severity of renal disease inclusion. Should you really need to study dialysis patients early on or not? Should you really be driven by timing? Do you need to have that information before the clinical trial?

I think when we're thinking about use of these alternate paradigms like PBPK versus population PK-based methods, when you're thinking about PBPK methods, I think one of the concerns is do we really have enough evidence that documents that this bottoms-up approach can really replace these well-designed controlled experiments?

When we think about population PK approaches, I think one of the challenges is that the population PK approach may end up defining a

dosing strategy that was not actually studied. So the disconnect there will be a definition of a potential dosing paradigm that wasn't studied in phase 3, from which we have to base a judgment. I think we're going to get pushback from clinicians saying that dosage was not studied, so why would we want to use that dose in practice?

DR. CARRICO: Jeff Carrico, NIH. First of all, I'll say I'm in general support of the direction we're going here. It would be nice to have guidelines in this population, et cetera. But I think back to contamination issue that was mentioned earlier that might cause industry to have some reservations about this.

I wonder if there might be some consideration -- and I'm thinking back to the simplicity and complexity comments at the introduction, but sometimes maybe we have to head towards complexity to get to the simplicity first. I wonder if there would be some consideration to viewing AEs in kind of almost a categorical approach; that if patients with decreased renal

function where were considered to be included in the trial, then maybe there could be some delineation of AEs that seem to be associated with that so that it doesn't go on the general list; like you said, a competitor may luck out of not getting.

I wonder if something like that, almost a subcategorization, could be considered, and that that might lead towards the simplicity at the end by encouraging the use by industry.

DR. KRAFT: Walter Kraft, Thomas Jefferson University. Part of the discussion is about a knowledge deficit for exposure and drug use in a renally-impaired population. I think part of the current paradigm is shifting some of this risk to actual use rather than in the context of a clinical trial.

One of the arguments would be that real-world evidence, perhaps we could use that data. I guess the problem with that would be compared to waiting for actual use will be a voltage drop in terms of the information that we

would get from otherwise including it in a drug development paradigm, and that in actual use, using the drug without guidelines can be one of two things, a clinician's need for therapeutics to make decisions with eyes wide open if there's no data or a clinician not really paying attention to things like renal insufficiency and worrying about the quality of that data.

I guess my main point would be for the FDA, whose goal is to work on societal health, using and shifting that knowledge acquisition into the controlled trial space probably makes more sense at a lower societal risk, in my opinion.

DR. DOWLING: Tom Dowling, Ferris State. Commenting on the discussion question here, there's a clause in here about without the need for a stand-alone renal impairment study. I guess my feeling here is that we really still do need those stand-alone renal impairment studies early on in drug development. I certainly agree with gathering data on real impairment in the subsequent phase 2 and 3 trials, but I don't think we can get rid of

the stand-alone renal impairment study that's going to at least guide initial dosing for the subsequent trials.

I don't know if that clause in that discussion question is for us to comment on, but I don't agree that we can take out the stand-alone renal impairment studies.

DR. MADABUSHI: If I can just clarify on that aspect, the intent was not to totally get rid of it when we were crafting this. We were thinking most of these studies are done pretty late in the development program, such that they are not informative. It may also be possible that the kind of characterization these stand-alone studies provide, one may be able to obtain such kind of information to alternate the approaches early on. Maybe those become stand alone for some subgroups, which early characterization was not possible.

That the context in which -- there has to be some efficiency gain. If we are doing all of the things, then we are asking something new; can we gain an efficiency by either taking another part

of that stand-alone expectation or somehow enhance it such that our uncertainty decreases. That was the thought process, just to clarify.

DR. DOWLING: Just to follow up to that, it's really the design of the stand alone that I think is still needed, so the single dose, extensive PK as opposed to a PopPK. The rigor of that individual single dose PK study I think is still needed.

DR. FINESTONE: Thank you. Sandra Finestone, consumer representative. I would just like to add to the discussion from a patient perspective that one of the most frustrating and disillusioning thing about being a patient is the exclusion of participating in trials. If you are end-stage anything, you almost always are not included.

I would suggest, for consideration, that not just the clinician's perspective be taken into consideration, but the patient as well. And I completely understand about the importance of the clarity of the data or the -- I don't want to use

the word "simplicity" but the pureness of the data. I understand that and appreciate that. But please consider the patient perspective, and particularly the devastating effect of ineligibility in trials. Thank you.

DR. COOK: I'd like to play FDA and respond to Tom's question. I believe it was in Richard's presentation from the IQ. We showed a graph that showed prediction versus excellent intensive study that was pretty good. How much information -- this is the one I struggle with -- do you need to be convinced that the stand alone might not be needed, that you can predict it otherwise? Because that would allow us to be able to start to think about inclusion of patients in the trials.

DR. ZINEH: Just piggybacking on the issue of inclusiveness, when Dr. Graham was presenting his paradigms, there were four of them, and all of them have the potential of offering direct benefit as oppose to what we currently do now, which is an interesting sort of perspective that we hadn't considered before.

I'm wondering if anyone on the committee would like to opine on any of those four specific approaches, whether it's a sequential approach, adaptive phase 2/3, a substudy of the phase 3 trial or the open-label extension enrolling patients with varying degrees of renal dysfunction.

DR. TENJARLA: Srini Tenjarla, industry rep. I think all of them have merit. I think on an individual basis, one may be better than the other. But in general sense, I think the adaptive design probably is going to add a lot of value to it as opposed to the sequential one. I can go into the details, but I want to hear from some of the other panel members first.

DR. SUN: Duxin Sun, University of Michigan. I think I already applauded FDA for moving in this direction. This scientifically will make a lot of sense and make a lot of better sense also. This adds some complexity, and at the same time, I also agree you need to give the sponsor some initiative to move in that direction. Not only the new direction you guys are moving, and not

only address the PK issue, which we were only focused on that; in addition to that, we really add on the PK and PD together, efficacy and toxicity. This is really a good idea.

Regarding the criteria, early in your slide, you asked what are the criteria we should use. I think clearly the 30 percent renal -- the renal elimination of more than 30 percent perhaps is very clear. Then I think we also needed to define for non-renal clear drug. It's too fuzzy. It's not there, should there; what is the criteria we should use?

To me, I'm thinking it maybe comes back to your question of when is the good time. So I liked Richard's proposal. I like the subpop group. In that way, really, the timeline should be maybe after the mass-balance study. You have enough information to really see that in that mass balance, do you have an unknown metabolite, or do you have a major metabolite with unknown toxicity function? Because that will give you information to decide and make criteria to say even if drug is

not renally eliminated, do you have a concern based on the mass balance? Then make a clear criteria there to see which one you need to do that and which one you don't. That's number 2.

Number 3, to come back to the volume distribution issue, for some of the drugs, that's perhaps is going to be important. Many drugs don't. For some of the drugs, especially, I don't think it's a toxicity concern, but rather the efficacy is a concern. Many patients will change volume distribution for some of the drugs. That may change the concentration. The AUC may not change, clearance may not change. But then you start having an efficacy concern.

So I think maybe also define some of the criteria there. I think the community, we are missing that area, how do we use it and what are the criteria?

To come back to the contamination issue, I think the real concern is there. If I include all those patients, what if all of a sudden I see a toxicity? That's going to kill my program, so

that's a real concern. I don't know if it's feasible. The FDA guideline gave the sponsor some initiative to say okay. Maybe the subpopulation study, I don't know, maybe predefined what is the population, you leave relevant data separately or rather lump them together. Otherwise, the real contamination is going to be there. If I were the sponsor, I would be very hesitant to take that risk. So that's the comment I have.

DR. MORRIS: Ken Morris from Long Island University. Following up on that, and I'm ignorant in this issue, if you make that for renally impaired patients, does that mean that you're also going to have to do it for hepatically impaired patients or other subgroups?

You're smiling, so I'm assuming --

DR. SUN: Quickly, I also agree with that. If you require this additional study, which is more complex, more scientifically sound, more timeline, more found, you have to reduce some other study in terms -- hopefully this answers some of the questions. Otherwise, you keep adding stuff.

DR. MORRIS: Yes.

DR. COOK: I'm going to put a plug, as I've just been thinking about it, today for the open-label trials, long-term safety trials, because the N is so much larger there, and you're more likely to get enough people in there to make that, rather than picking one efficacy trial that may only have a few hundred in a group, and you're talking about a subpopulation to that.

The challenge will be, as with all open-label trials, that we don't run the comparator population even though we should. So maybe we ought to get better at using external data for studies to use as that comparator, with all the problems that go with that. But we need to somehow get better to have that comparator group so we don't have to worry about small N's and what we might or might not see in a comparator group.

DR. TENJARLA: Srini Tenjarla, industry rep. Maybe I'm trying to look at a practical solution here because, to me, I get the feeling that everybody's in agreement that we should

probably look at a multi-pronged approach, but we keep circling around the same thing, investigating the specifics of what exactly we need to be doing.

So maybe just to start the discussion, I would probably say we have the preclinical data. We know more or less what the PK looks like. We know that every molecule is going to be different and how it behaves. Start from there, and then look at the various options that are being presented today, and then come up -- look at each of them, evaluate all of them, what design you're going to take.

Maybe you want to do an early PK study as opposed to your stand-alone late PK, which is not going to add value to that. If you do an early PK study, you get a read from that, and that is going to be very useful for you to design your phase 3 programs, and so on and so on.

I think it will be very good that once you look at the three or four options that are represented -- and maybe there'll be some more. But at least look at all those options, and if

there's an opportunity to talk to the agency and saying, look, here's the merit or the disadvantage of option 1, 2, 3, and 4; this is what we would like to propose.

I think what it does from an industry perspective is that it gives you a warm and fuzzy feeling that you're going in the right direction as opposed to shooting darts in the dark.

DR. THADHANI: Thank you. I also want to congratulate the FDA for bringing this topic to the front. I'm going to make some general comments and then some specific comments. The first one, I think we've spoken this afternoon and this morning, certainly about the limited sample size.

Kellie nicely showed, as we began this morning, that 20 percent, or thereabouts, of patients in the hospitals today suffer from kidney disease. So while it is a small sample size as you get to the later stages of kidney disease, it is not a small sample size, in general, of patients that would be affected by the decisions of this committee and others moving forward.

The second point I'll make is that we talk about end-stage renal disease being different, and there's no question end-stage renal disease, those patients have differences between patients in stage 3 and 4.

For somebody who's done phase 1 studies in end-stage renal disease, it is incredibly difficult. There are not many phase 1 facilities in the United States that even accommodate end-stage renal disease patients, not the least of which allow dialysis machines to be moved into these facilities, so you can actually do long-term PK studies.

Then we might argue that maybe we should get information from patients in stage 3 and 4 because those patients are abundant, so to speak, or at least more available. For the few of us that take care of these kinds of patients, in stage 3 and 4, they are contemplating a complete change in their life. They're contemplating a complete change in every aspect of their life, their work, their personal relationships, multiple medications,

in addition to multiple comorbidities.

So to ask these individuals to participate is not straightforward either. But that said, we have to encourage sponsors and we have to encourage patients. So the question is do we actually go to these late stages or encourage sponsors to get some early information short term early on; not maybe because there are more patients or less patients, but because it's a very different time in the stage in this person's life, if you will, in terms of their career. I hate to use that word in kidney disease.

So with those general comments, there are some specific points I'll make. One is the older guidance documents of course highlight methods of GFR measurement, and perhaps the nephrology community has sort of shot themselves in the foot and have changed formulas and changed measurements of GFR.

I think at some point, we might as well just agree on a formula and move forward. We have PK studies that have been done in patients with

kidney disease with older formulas, and now we have new formulas, and they don't necessarily talk to each other, and everyone advocates for one. I think that debate, as long as academics are in business, you'll continue to see that to change. That said, I think we might as well just agree on a formula and move forward. And whether it's completely correct or not, at least it gives some guidance and simplicity to industry as well as academicians.

The second point, I completely agree with what Dr. Sun said. In some way, if there could be -- not to limit transparency but some encouragement, so that there is not so much of a penalty, if you will, for gathering early data in a drug development process, especially if there's a primary goal of a general population and the sponsor's willingness, if you will, to look at this patient population. And again, I leave that up to the agency.

The final thing I'll say is that there are a number of people, in academics as well, who

submit to the FDA IND exemptions to participate in clinical trials, especially those individuals with kidney disease and asking for altered, for example, dosing regimens, and as a result have to request an IND exemption.

The current guidance for IND exemption today is that if you don't change the dose, you don't change the route, and you don't change the indication, then you're able to get an IND exemption. With those kinds of criteria, it is very difficult, as you can imagine, to encourage anyone to put forward an IND exemption request.

If there were words in that kind of document that said if the doses were going to be lowered because the PK may be changing in patients with kidney disease, that would encourage more, if you will, academicians and industry sponsors to pursue a better understanding of PK in this population.

DR. LI: I actually have general comments. I think this is really an important issue, and I thank FDA for raising this issue again after a

decade. I do see this, again, as a complicated issue, but it's important. I think the question here is whether we should recruit the patient in early trials. Personally, I think we should. In a way, it's also kind of like a chicken and egg question. If we don't include those patients early on, we could not get the information we need in order for drug development.

Again, looking at this question, this morning I think we really mainly discussed is whether we should include those patients in clinical trials. I think at this point we are not there yet to discuss what kind of alternative strategy we're going to use to bring those patients into the clinical trials.

This again is my major comments, and I really commend FDA for bringing this important issue up. Also, the specific comments I have for this study, I think this is also related to maybe the second question we discussed. Personally, I think the underlying hypothesis for this study is that renal impairment is directly related to the PK

clearance, and then from there, it may impact on efficacy and safety.

But I also think there might be another complexity that has been also raised by FDA and also by the other presenter, and that is that renal impairment could also impact maybe metabolism, transporter, and other issues as well. So I think, again, it is not a simple question. But from a development perspective, there's definitely a need to bring the patients as early as possible to learn this information, and it may help, again, to facilitate both drug development and also patient care as well.

DR. COLLINS: There are two issues we're concerned about. One is the increased exposure when there's reduced renal elimination, but that's the next topic, so we'll skip that. But I have to follow up on Dr. Li's comments.

I'm concerned that we're focusing too much energy on the fact of whether a patient with impaired renal excretion, other than end stage, is inherently more sensitive even to low levels of the

drug. To be consistent, as mentioned in Dr. Reynolds' slides, right now our criteria is that there's no dose reduction if it's known that 30 percent or less than 30 percent are excreted in the urine.

That's inherently saying that we've already made a decision that the interaction with transporters or metabolism are not a major issue. It doesn't matter whether it's 30 percent excreted or a hundred percent excreted. We've already addressed that issue.

That's not the way I necessarily expected this to come out at the beginning of the meeting, but I haven't heard anyone give any cogent reason to think that we need to focus a lot of brain power on those issues that we keep raising in general senses without any data.

DR. MORRIS: Ken Morris from Long Island University. One aspect with respect to a comment on the aspect with respect to patient inclusiveness is that given the dearth of drugs that are available to treat general kidney disease, any

potential inclusion that might show up a positive side effect also would be more than welcomed by kidney patients, speaking personally; so just a comment.

DR. FINESTONE: I just wanted to add something. I didn't disclose before, and I should, my husband's on dialysis, peritoneal. I can tell you that not only has his life been impacted, but so has mine. Things have changed dramatically for us. We participate in conversations with other dialysis patients. I'm speaking for them, and I probably shouldn't, but I think that they would be very open to participating in clinical trials. Their lives are on the line, and there's also an empirical kind of thing to want to help out their patients.

So this issue of the N I think is larger than you might anticipate, and I would be extremely grateful if there was some improvement. Any improvement would be welcomed.

DR. TERZIC: I think we're now going to the synthesis stage for this first question. Our

colleagues will be taking notes and trying to synthesize what we'll be saying. I'll try to use my voice to speak your thoughts, but correct me as I go forward because I may have forgotten what you have said. It may be a little bit convoluted. But I think the goal here is to have, as clean as we can, advice to the FDA.

I think what collectively you have said and what has been also supported earlier this morning, to use your word at the very beginning, this is really an opportunity, and the opportunity is really related to the path of demographics that have dramatically changed. The number I think is important to re-raise is that 15 percent of the population will suffer of some type of renal impairment. If I'm correct, the numbers that were moved forward were around 30 million Americans that will have renal impairment. That is I think a starting point.

The second point that was raised was actually a thank you to the FDA and a congratulations for bringing it together. I think

that everybody recognized that importance and the timeliness of doing it.

I think the third point, and I will honestly start there, is the patient's unmet needs. I think the patient's unmet needs and the perspective of the patients here are very important in guiding us. It was reflected in the concept of end-organ disease and the need to be integrated in this process as much as possible.

These are some starting points. If we now zoom in, I think to be the most systematic, probably the opportunity comes from another discussion around cancer guidelines, and we can maybe use them as it were presented, that essentially the March 2019 update for cancer therapeutics does include the discussions on renal impairment.

Related also to our nephrology colleagues as they defined this, it appears that the glomerular filtration rate is the golden standard today, although there may be different formulas. But it is a golden standard in defining renal

impairment. There may be different definitions, but one definition in that spectrum may be useful because that will stratify the patients in different ways.

I think the other concept that is there, but also you mentioned it throughout, is the totality of experiences that has been raised many times. Really, the idea there is how we can balance risk versus benefit, having the totality of that.

The other aspect from the cancer ruling that was mentioned is the timeliness of severity. Are we really focusing on more advanced cases or are we looking at renal impairment in totality? Then finally, the concept of dosing regimen that you have mentioned and Dr. Collins also has mentioned as well.

Those are maybe frameworks that are helpful. The interesting idea that were raised from our colleague in Thomas Jefferson is this concept of knowledge deficit, and that knowledge deficits may in a way guide us to use more standard

forms of clinical testing to fill that gap rather than the real-world experiences. So there was that appeal to maintain us within the more standardized clinical trials.

Are we doing good with the notes? Okay. Are we doing okay so far? Okay.

What the FDA reminded us is they really will like our opinion on the paradigms that are presented. I think, if I heard collectively what you said, nobody has really put forward the sequential approach, which is the first paradigm. I think there were positive indications for the adaptive design as a way to keep on learning, and I think new knowledge into the process as well as for the subset example, which was a way to add additional knowledge as we move forward.

Those two were primarily mentioned. There was some interest for the open-label design because of the number of individuals that then can be accrued in that way, although there were comments that may be the N is not so much of an issue. So I will let's say keep more emphasis on the adaptive

design and the subset renal impairment paradigm, although the open label may conflict a little bit with what Walter was saying in terms of real-world experiences.

A nice concept that was also mentioned is a multi-dimensional way. In other words, there may not be a singular option for everybody, but rather multiple options that should be put forward and then defined on a case-by-case basis.

Let me stop for a moment here, and again ask you if there is something that we are missing that you would like to reiterate? Remind me a little bit of what you said.

Please? Our statistician is now speaking, so let's see.

DR. SLUD: Eric Slud, University of Maryland. It seems to me that the knowledge that's being gained in including these renally-impaired patients in any way is meant to contribute to a model, which simultaneously talks about population-wide pharmacokinetic effects, but also those effects that are modified by the renal

impairment.

Whatever in the design aspects, whether adaptive, sequential, that can be analyzed within the framework of such a model is useful for the end goal of predicting dosages and modifying dosages. In deciding among the different patterns of design, the patterns of adaptive or modified clinical trials, some of them are a little bit complicated for analyzing within the formulation of such a model, and to that extent maybe ought to be down-weighted for that reason.

DR. TERZIC: That's an important addition. So in other words, to be very firm into what is to be expected in any of the models that are being picked up.

Any other comments? I think the main discussion is really about the right early dosing and is a critical information gap that exists right now, and how to enhance the appropriate early dosing has been raised many times.

Please?

DR. NOLIN: I'd like to comment on that. I

think a sequential design with some minor modification might be able to address that. I was going to make this point earlier. First of all, I also would like to applaud the FDA and Dr. Graham for putting these forth. I think they overcome a major limitation that we've had historically, which is a lack of dosing safety and efficacy data in patients with kidney disease in larger clinical trials, when they're being treated for something that may not necessarily be the kidney disease itself. So I think that this is an enormous opportunity that I'm glad to see FDA pursuing.

I would suggest that the sequential design is an opportunity, perhaps, to address some of Dr. Dowling's concerns, which I also share, and that is to have early legitimate, intensive sampling, which is required to determine PK in most situations, in order to inform subsequent models.

I think that with the sequential design as depicted in this slide, there's an opportunity to do that, particularly in the aspect of the slide that relates to subjects in whom is a greater than

2-fold increase in systemic exposure. It seems to me that in these patients in whom there's already a proposal to reduce the dose, that is an excellent opportunity to embed in these trials some intensive sampling to determine what the PK in corresponding dosing requirements are to satisfy what we're talking about here.

At least as I understand it, as it's currently designed in a phase 3 clinical trial, there is no intensive sampling. There are no PK studies that are embedded in these studies typically, and I don't see that in this sequential design here. But I think with the addition of that, we could glean data that would satisfy lots of things. It would satisfy the pharmacokineticists in the audience to be sure that we've informed the appropriate dosing.

We also would have legitimate safety and efficacy data after multiple dosing in patients who are being treated for the intended purpose. So I think it really could be a win-win of this type of design where adaptive.

The last point I'll make relates to the notion of assessing renal versus non-renally clear drugs, and when do we do this. I would propose that we should be agnostic, and we should be exploring, for example, a sequential study design where we are embedding patients with kidney disease in all of these trials, regardless of whether the drug itself is a substrate of a non-renal pathway or not. That's all I'll say.

DR. TERZIC: I think the only real revision, then, is to ensure that the sequential approach also has its merits and potentially should be considered. Again, kudos to the IQ group that all 3 and a half, maybe even all 4 models, have not received too many negatives.

Any questions before we close in? We need to move to a number of other questions. Please?

DR. DOWLING: I would just add to Dr. Nolin's comments that I really liked that thought of a PK design subset of patients within the sequential, and also a proposal to potentially measure GFR in a subset of these folks using like

an exogenous alpha-aminohexyl. I know EMA is doing that and recommends that in their guidelines as well. So just a thought on a subset there as well.

DR. TERZIC: One last question?

DR. NACHMAN: It's not really a question, but in your summary, you didn't mention Dr. Thadhani's suggestion of somehow facilitating, even on a post hoc, the ability of doing PK studies in patients with advanced kidney disease through IND exemption or other processes.

I think this is -- to include Dr. Finestone's comments, in a way, we're doing trials without controls and without the safety of the trial every time we use a drug on those patients without really knowing anything about the dynamics and the kinetics. So the more data we can get, the safer it is for the patients in the long run and would much rather get the data first than doing it on a ad hoc basis in the ICU.

DR. TERZIC: Thank you. There is one more question.

DR. DONOVAN: I'll try to make this quick.

I am still thinking about Dr Morris' first comment about doesn't this really actually extrapolate to hepatic dysfunction, cardiovascular disease, and all sorts of patient populations that are excluded from trials typically because, again, we want to be able to be as certain about the results as we can and not have comorbidities conflicting in our data analysis.

So in trying to think about that and listening to others asking for additional data to be able to be collected in real time along with some of these study designs with just the renal population, I think it begs the question on how the FDA perceives subanalysis in an ongoing phase 3 trial; that questions about blinding came up, being able to do interim analyses and so forth.

I think in order to get at efficiencies and to get at sponsor willingness to look at these very important populations very early on, defining some criteria and some opportunities for sponsors to do subanalyses early during a trial and the FDA developing some criteria for -- if this is the

result and, it looks like there is going to be more concern for renal disease or whatever other disease, these additional studies would be good to conduct during those trials, whether it's an additional PK, whether it's more advanced disease, or whatever it turns out to be. It also allows that identification of this probably won't be an issue with this particular drug in this dosage range.

So I think the trial design -- I'm talking a little bit more adaptive, but I'm also talking some subgroup -- that in order to not have this only look like it's only serving the renal issues at this point and coming back in three years and having another meeting that now is going to address hepatic and so forth and now make your lives even more complicated -- thanks, I know -- to broaden this before you take the next leap, even though I don't want to see that delay the opportunity

My sense is the sponsors are willing. They just need to make sure that there's a way to continue to be successful as they carry out the

trials, while they're also evaluating likely patient exposures.

DR. TERZIC: Thank you very much. For the record, the inclusion of the concept of actually IND exemptions may be important, and also the concept of comorbidities. Comorbidity is a big, obvious issue. Today we are discussing renal impairment through a single parameter of GFR. But looking even at what has been mentioned, let's say, cancer patients -- and we didn't mention at all the diabetic patients and hypertensive patients -- are clearly very critical comorbidities, and whether at some point, we will need to be much more cognizant of the comorbidities in the context of this discussion, and may come back in a more vigorous way.

Shiew-Mei?

DR. HUANG: I just add a clarifying question. When we were discussing sequential approach, I think you mentioned the agnostic to elimination pathway. Is that what you meant? Either the compound is mostly renally cleared or

mostly metabolized, you would suggest the sequential study is necessary.

I was just wondering, we also talked about totality of evidence, so before you do this study, we do a phase 1, and we might know the pathways. For example, if the drug is completely metabolized, you would still say there must be other factors. So we need to do mild, moderate, and severe instead of what we're thinking, the severe group's is the one that we will see.

In our experience, the more clinical studies you do, the more variable outcomes you may see. Here, the normal group and the other subsequent analysis also is a normal group that you may see a quite different clearance considering the study site and other factors that may cause the variation.

DR. NOLIN: Yes. Let me be more clear. Having just thought about this as I'm seeing this today, bear in mind, I suspect there's a way that we could sort of adapt the reduced design into this approach, where the intensive plasma

sampling -- for example, the traditional PK design or assessment -- is incorporated into this.

It's not clear to me from this whether this suggests that all of the subjects that are enrolled, regardless of kidney function, are having intensive sampling. Is that what was proposed in this design? If it is, then I agree with what I think you're suggesting, Shiew-Mei, and that is that perhaps we could adapt what is currently the reduced design into this.

However, I think it's critically important to continue to enroll patients with all degrees of kidney function, including mild renal impairment, even if we're not conducting a full PK study because it's important to have safety and efficacy data in these patients regardless of what the drug is for the treatment of kidney disease, specifically or not.

It's important to have patients who reflect the general population in whom that drug is going to be used, which currently kidney disease patients currently are not included in these studies but are

very commonly receiving drugs for which they weren't included in the clinical trials.

So there are a couple of issues I think that could be embedded into design, not the least of which is the assessment of renal impairment on PK. And perhaps we adapt the reduced design into, again, a greater than 2-fold exposure or something like that. I think the details would have to be worked out, but I think there's certainly a way to tailor it.

DR. HUANG: Yes, I agree, the details need to be worked out because I look at all four approaches, which is to enroll patients in phase 2 or 3. But the trials could be cyclical [indiscernible], but I don't think that we have discussed that at all. Correct?

DR. TERZIC: At this stage, we will bring to closure the discussion for question 1 because we have several other questions. But we'll come back, maybe at the very end, to ask the FDA if they received the information they need and what additional information they would like to receive

from the group.

So as we move, it's still labeled here as question 1 but topic 2, so maybe we have addressed, maybe not. Please discuss if it is reasonable to assume that the drug's exposure-response relationship will usually not be significantly different between patients with impaired renal function and patients included in the registration trials, and the situation where the assumption of similar exposure-response relationships may not apply.

Who would like to start? Remember we can modify the language -- we cannot -- if there is any clarification of the intent of the question.

DR. ZINEH: Is there a need for clarification of the intent? No?

DR. TERZIC: Dr. Collins?

DR. COLLINS: I just generalize it to say that exposure matching is the default option for any special population. We've had some discussion about that throughout the meeting. Some of them are harder than others, so it's easy to measure

renal function elimination. Hepatic is a little tougher, but there are many other subpopulations that are out there that are challenges when you're setting your entry criteria to clinical trials. I think that the success of exposure matching across the board gives us more confidence that that's the default option.

DR. TERZIC: Please?

DR. SUN: I feel only the parent drug is actual moiety or if it's a known metabolite. If we know its function and it will also measure PK exposure, perhaps most likely, the exposure-response will be fine, which you presented in the first case.

My impression would be if you have an unknown metabolite, which is significant enough, or you have a known metabolite but you really don't know its toxicity profile, that may fall to your scenario 3 or scenario 4, and that may not be true. I think in that sense, the mass balance study perhaps will give you a lot of information. I think that's the decision point to make that

determination, although you still don't have a function of the metabolite.

I feel this may be more important than the other aspect, especially for the drug, which is liver metabolism. If the metabolite has its own toxicity profile, the PK accumulation, it may very well be renally eliminated, although the parent drug is liver metabolized. So those perhaps we need to particularly pay attention. That's my impression.

DR. TENJARLA: Srini Tenjarla, industry rep. From my point of view, I think for most of the drugs, there will be an exposure-response. I think it's a fair assumption to make, but I think there will be exceptions in certain cases, maybe severe liver disease, comorbidity, and so on and so on.

That's the reason why, as we just talked about for the topic number, the previous question, when you have an initial read from your PK study earlier on in specific population, like renally-impaired population, that will give you a

better feel in terms of answering the second part of the question, that there may not be necessarily exposure-response specifically to that particular patient. In other words, in most cases applied, there may be exceptions. If you are prepared to understand sooner how we can identify the exceptions to the exposure-response, that will be great.

DR. NOLIN: This may be obvious, and forgive me if it is, but the classic teaching in pharmacology with respect to what to dose -- or the exposure-response relationship will change in patients with kidney diseases is with highly protein-bound drugs. Many of these are non-renally cleared, and patients with kidney disease become progressively more hypoalbuminemic typically as kidney disease progresses, with the exception of glomerular nephritis patients in whom oftentimes the eGFR can be quite normal in fact, particularly within the context of what we consider the GFR categories; yet they can be profoundly hypoalbuminemic.

So what that means is that if the sponsor or any clinician is measuring total drug concentrations, they may think the systemic exposure is unchanged when in fact the active moiety may be profoundly increased, and therefore the response is going to change. That's the classic scenario where we might see a difference in the exposure-response relationship.

DR. COOK: I will assure you it's standard practice in renal impairment study studies to measure protein binding, so we do get that information to examine. That's at least one instance where we do measure free drug.

I guess on the question of whether it's reasonable to assume something, I think my bias is it's reasonable to assume it, but you guys across the table from me have always drilled into me the lack of evidence is not, in essence here, evidence that it's lacking. So I will say it with that caveat. I just don't think that it's systematically been looked at to see if it changes. I think we can just go by anecdotal, and I don't

see a lot of evidence that it does, except in instances where it seems like it should and it does, for instance, when it acts on the renal tubule.

DR. SLATTUM: I actually agree that it's probably a reasonable assumption because we've been making it, and it most of the time has worked out okay as far as we know. But thinking about how we could challenge that assumption earlier to know, I think some of these designs that we talked about might allow that very thing. Then we end up knowing when we need to do something different rather than just hoping it works out okay in clinical practice.

DR. MADABUSHI: I think Dr. Slattum, actually addressed -- my question to Dr. Cook would have been, given that we have heard that we should be more inclusive in late-stage trials and there are ways to go about it, would it be reasonable to assume these exposure-matching principles? For inclusion purposes, it seems pretty straightforward. The uncertainty is when we are

going to derive dosing recommendations without any other additional information, given the caveats that you described.

DR. LI: Tonglei Li, Purdue University. I don't have a question for this issue, but just comments. I think when we look at exposure-response data, I think we need to keep in mind that drugs are given as product, as a formulation. If we use the same drug but a different dose, the manufacturing process or the formulation could have the impact in the absorption of the of drug.

In some case, if you do an LC [ph], like linear response amount different in doses, it's not because of, again, this relationship. It could be an absorption process. Also, this issue may play a more significant at a later stage of development because at that stage, I think the formulation and manufacturing process are probably already finalized or maturely studied so that when you give different doses, especially for modified release or controlled release, I think the manufacturing

process or formulation could have a indirect impact on this relationship; just a comment.

DR. THADHANI: Just to go back to this particular question, specifically the response, and I want to echo a comment that Srini made and also what Tom made. I want to bring up the issue, which I think is important, of the African American population as we go and estimate kidney function and then the dose response issues. Just by way of example, again, given our differences in formulas, and again, we're responsible for that as a community. The reason we have four of them is because none of them are perfect.

With that said, when we have an African American with a creatinine of 1.7 and a Caucasian with a 1.4, and you put these two individuals with two different creatinines into a variety of formulas, and you then superimpose upon those formulas, these fudge factors that we've included, those two individuals have the same GFRs.

So that's what we're using to make our decisions on which patients we include or not

include in dose response. But when we look at those two individuals, the severity of comorbidities is actually quite different. Even though the GFRs are similar, there are differences in left ventricular hypertrophy, blood pressure, uric acid, hemoglobin, and so forth.

So I think it's important, going back to this issue which is exposure-response, that even at similar GFRs, where we think we've cleaned it out and necessarily homogenized the population, especially when it comes to African Americans in this country, we have differences in comorbidities. When we think about response of a drug, not just on kidney disease, but their related comorbidities, there may be differences in effect.

DR. TERZIC: I don't see any more questions or comments at this point. Let's try to summarize topic 2, question 1. We can start really with what Dr. Collins summarized for us, is this default option, just to quote his words, and the cost of that exposure matching typically applies across the board.

Then we had the statement -- there was a call really for systematically obtaining evidence that potentially are linked to deviations to this umbrella approach. So the deviations that were mentioned -- again, in not specific order, but let's say the parent compound is metabolized through the kidney in contrast to, let's say, the other metabolites that are metabolized through the liver was one potential area of concern.

The other areas included comorbidities in general that can affect significantly the exposure-response. The protein binding of drugs was another area that was mentioned. An interesting area of formulation was also mentioned as it impacts, for example, absorption, and then related to that the destiny of a drug.

I think the last comment was particularly important to underscore that different severity of manifestation of disease is an important component in this aspect to keep in mind, especially if it's related to the diversity of populations and despite let's say the GFR being equal or similar.

Particular attention to African American populations have been exemplified in this discussion.

Please?

DR. ZINEH: Can we clarify the last two points in terms of how that could be operationalized into a rubric? The problem is that when we say comorbidities could affect exposure-response, that leaves open an entire universe of hypotheses. So we can't pin down what those comorbidities are. So if we wanted to kind of parlay this into a rules-based or a risk-based approach -- the others are very clear: high protein issues around metabolite -- how might we deal with the issue of comorbidity?

DR. TERZIC: For the FDA, please summarize what could be the comorbidities of highest importance? I think that's a starting point. So please, there is that element, maybe from our colleagues that deal daily with patients with renal impairment?

DR. NACHMAN: I'll take a shot at it. I

think that the cardiovascular risks are at the forefront. Thadhani mentioned, especially as we're going down the line of more severe renal impairment, there are issues of bone mineral metabolism. There are issues of bone marrow toxicities that become very salient. A drug that may have an effect on hematopoiesis, for example, can have a far more drastic effect at the GFR of 20 than a GFR of 30 or GFR of 15.

I don't know that I can cover everything, and I don't know if you can think of other ones. Certainly, it would have to be addressed more or less on a case-by-case basis, based on what is a suspected to be relevant to an individual product, but this is the kind of stuff that becomes disproportionately more important at the lower GFR ranges. This is the part where I worry about the extrapolation from moderate GFR to a low GFR based on exposure, based on GFR alone; so the pathophysiology changes.

Please?

DR. KRAFT: Walter Kraft, Jefferson. In

terms of comorbidities, I would see that primarily as a issue around safety, and it doesn't get necessarily to the primary hypothesis, first principle about exposure-response. So I would say that the comorbidities that travel as covariates with decreased renal function and are different between different populations will manifest in safety but not necessarily in an efficacy endpoint. The price you may pay with the comorbidities that are unmeasured is increased variability, and that may be just the price of doing business to get the inclusion of these populations.

DR. THADHANI: I'll take a stab at what Patrick started. Let me give you some concrete examples. Recently in the nephrology community, we've identified a genetic risk factor among African Americans in terms of progression of kidney disease; in this case, a particular genotype, APOL1. When you look at those individuals with 2 copies of the variant, the acceleration of kidney disease in that population is about 1 and a half to 2 times faster than comparable GFRs in the

Caucasian population without those 2 variants.

If from a registrational standpoint you're doing a clinical trial where a reduction or a slowing of kidney disease progression might be an endpoint, as you can imagine, if it's a threshold effect, there may be differences when you compare races. On the other hand, if there is a percent difference, there may be more similarity, and that's just one example.

Another example could be when African Americans start on dialysis, their average PTH values are about 30 to 40 percent higher compared to Caucasians. Clinical trials today in reduction of PTH -- most of which are historical; we don't do as many today -- have been threshold effects, again, as well as percent effects.

So as you can imagine, if you take an African American with the PTH of 400, reducing that level versus a Caucasian who starts at a 250 and reducing that level, if it was a threshold effect of less than 300 or less than 200, you can imagine a Caucasian may meet that sooner than an African

American, as another example. We can make a variety of different examples in that category; blood pressure differences, when they start, baseline blood pressure differences. Patrick highlighted of course hemoglobin differences.

So I think the sensitivity around the diversity in terms of comorbidities, especially as the FDA provides guidance, taking to account the differences, individuals who may benefit the most, for example, African Americans for certain diseases, may not necessarily be excluded for the reasons that are put forward or may not meet thresholds otherwise that might have been a starting point as criteria.

DR. TERZIC: Any other needs for clarification? Paul, please?

DR. BERINGER: Yes, just one addition. Drug metabolism was brought up as one of the relationships where GFR may not accurately predict. The other is a drug transporters. So if the drug is a substrate for certain transporters, then that may not be picked up by GFR, the alter clearance.

This is particularly important if you have a patient who is on a drug transport interaction that may alter the relationship.

DR. TERZIC: I think for the record, we will add these two last comments, extending the metabolism to include the drug transporters status. With the comorbidities, I think to summarize them, one is really emphasis on very low GFRs where it's a particularly important domain, and then, actually, the concept that is common to all of these examples is as the chronic disease progresses and making sure what exactly the population that is being tested is. Typically we see some very generic definitions, let's say heart failure, but without really the understanding how advanced is the condition.

So when you ask how to operationalize it, I think that's very important, to be very definitive about the severity and the degree of progression of the comorbidity.

DR. THADHANI: For the record, I'll just add one point just to highlight what Andre said.

The goal of course not only is to just understand the variability, but to provide gold posts that don't discourage sponsors from including individuals of different races and ethnicities and diseases because of inherent differences of the ones that we've highlighted.

I don't know, Patrick, if you want to comment.

DR. SLATTUM: This is Patty Slattum from Virginia Commonwealth. I just want to emphasize one other group that is one of the fudge factors in most of these equations, and that's those at advanced age. Maybe when we're thinking about how age is included, we want to have more older persons in clinical trials, but really are we talking about aging or frailty? And maybe their chronologic age is not the right -- when we think about how we're measuring things about individuals coming into the study, it's not so much their chronologic age, but maybe some factor like frailty that's determining the outcome. I guess you could think of it like a comorbidity.

DR. TERZIC: Definitely, the concept of aging increasingly is not so much linked to the life span; it's more linked to the health span. So somehow to formulate in that sense would be potentially useful.

There is one last comment. Please?

DR. PAI: Just one last comment. I think when we're also thinking about this idea of impaired renal function, I think we're thinking in the context of CKD or chronic kidney disease. But obviously when you're doing these clinical trials, sometimes that judgment is not made.

So you're looking at someone's serum creatinine without the context of how they got there. Often when we think of anti-infective clinical trials, again, there are very clear case examples of failure in that group that's between 30 and 59 mL per minute, primarily I think because we're considering that individual to be in that group of having chronic kidney disease when they really are not patients with chronic kidney disease; so their function is actually higher than

what would have been predicted. Their clearance function would have been actually higher than what was predicted from the healthy volunteer trials.

So I think there's a little bit of a mismatch there, again, when we're thinking about patients because if you have a 90 year old with that serum creatinine, or a 20 year old with that creatinine that gives you that same GFR, those are different individuals, and sometimes that's missed.

DR. TERZIC: Yes, this is also important. We have seen it in other settings to be very definitive as to the clinical condition, let's say an acute failure versus a truly chronic progressive disease. I think that's very important.

If no more questions, we will take a very brief break, 10 minutes, and we will reconvene for the last two questions. Thank you.

(Whereupon, at 2:29 p.m., a recess was taken.)

DR. TERZIC: We will start our last portion of this committee meeting, and we will now zoom in on the last two questions.

We are proceeding with the following discussion. It states, often for exposure-matching purposes, the normal renal function group serves as a reference group. The FDA proposes the reference group to be selected based on the understanding of benefit-risk for the drug and be more proximal in terms of renal function, severe versus moderate instead of severe versus normal.

The FDA is asking for input on this particular question. Please?

DR. COOK: A clarification on this, and I'm going to use the example of 1.3 from normals to moderates, and then 1.3, again, for moderates to severe.

DR. TERZIC: Can you please speak more closely?

DR. COOK: Jack Cook, industrial representative. I in principle think the risk-benefit is fine, but another practical consideration is the dosage strengths that you have. If the increase was 1.3, you might say, well, if the next dose I had was 2-fold higher,

does it seem reasonable to then give the one, even though it's a higher exposure, and is safety going to be adversely affected? If you say no, then that would be the dose.

Again, if the next thing is another 1.3, if I'm doing my math right, that's about 1.69 or something like that, that would say that I should actually go to the next highest dose, practically, and that seems more reasonable to do it rather than just basing it on trying to match the exposure of the next dose.

I guess what I'm saying is that we typically look at the less than severe, the moderate, and compare it to what the change in exposure is in the normal group. Is what you're suggesting is not to use that anymore and just go to the moderate group, which is already based on the normal? I'm trying to figure out how I can jump with the dosage strength.

DR. MADABUSHI: Sure. Definitely the availability of strengths should be part of this calculus. The thought process here was -- maybe

I'll use an example to illustrate it.

Let's say there is a 2-fold increase exposure in moderate despite that they were included, studied, and found acceptable from a benefit-risk perspective. Now you have severe, which is 4-fold increase in exposure. If you were to compare with normal, you would want to do a quarter dose. Could you do halving of the dose in that kind of situation?

I'm just making it a very stark example to talk about choosing. Obviously, it has to take into account the availability of strengths and things, so should we always anchor to normal? If so, what might be the reasons for that?

DR. COOK: And the advantage you're proposing is that you've already studied it at that higher one in a population somewhat closer to it than the normals.

DR. MADABUSHI: That's correct. And this is under the assumption that more often than not, we might not have this full characterization of exposure-response across the entire spectrum, so

trying to go to the one which is most closest, yes.

DR. TERZIC: With this clarification, can we now address more specifically the question so it relates to the reference group, essentially?

(No response.)

DR. TERZIC: It's a quiet committee after the two questions. I need to more out of you. Please?

DR. SLUD: Eric Slud, University of Maryland. It seems to me that the intermediate group, the moderately impaired, would have been the result of a more recent estimation with far less data than you would have had on the normal group, at least most often. Therefore, you might have decided that there the dose didn't need to be changed, but that's really a best judgment based on a whole confidence range.

There might be considerable noise in that, and using that as a reference group makes the further analysis just that much more contingent on earlier analysis that's been done, while maintaining a reference group that's big and well

studied and numerous makes the final results more solid.

DR. TERZIC: Please?

DR. MORRIS: This is Ken Morris from Long Island University following up on your point. Does having the reference group that it includes the moderate or variously impaired patients make powering the study more difficult? Or substantially more difficult I guess is the question.

DR. MADABUSHI: Before answering, I was trying to understand the question. It's not necessarily always that moderate is already derived. It could be moderate was studied. It's also possible moderate was not studied, but maybe it could be matched to mild, which Dr. Cook was presenting, but it was plausible within the strengths.

DR. MORRIS: I think actually it's a simpler question. It's more falling on the statistical analysis that if you set out to have a reference group that has a mixture of normal to

variously impaired, does that make it more complicated to not just recruit, but does it make the numbers larger? I don't know.

DR. MADABUSHI: It shouldn't be expected to be any different than what we will do.

DR. COOK: Now I have another clarifying question. I was presuming that you were trying to generalize them to a case where you may not have a prospective study or anything. You're just trying to come up with dosing recommendations to a group you may have PK on but no PD on. I've done the phase 3 study.

I've done the single stand-alone renal impairment. How do I figure out the exposure I want for that, or the dose I want for the most severe groups? I may have studied people in my phase 3, like most of them there where they have mild or moderate renal function. Is that the better comparator group to try to match, or is it better to try to match that to the normal group?

Is that what you are saying?

DR. MADABUSHI: That's correct. That's the

question we are asking.

DR. MORRIS: Thank you. That clarifies mine, too.

DR. TERZIC: Ravi, I think you had a follow-up question.

DR. THADHANI: Just a comment. If you do a large clinical trial of 10,000 people, whether you like it or not, you'll have about 20 or 30 percent of people in that population with some form of kidney disease. You can't get rid of them, because of the prevalence of the condition. That's the first point.

The second point is that we're looking at cutpoints to define severe, moderate, mild, and so forth based on a continuous variable, all of which has tremendous variation. So in one formula -- I hate to go back to that point -- they're considered mild, in another one, they're considered moderate, and in another one, they may be severe.

So inherently, when we're looking at this particular point, yes, we'd like things to be clean and say we're comparing severe to moderate,

moderate to mild, mild to normal. In a large enough sample size, you will have tremendous variability. You won't have the extremes, meaning you won't have severe, but you'll have quite a bit of variability.

Apropos, for example, the SGLT-2 trials that everyone is familiar with, when they first started, their exclusion criteria was significant kidney disease. But whether you liked it or not, many of them had some form of kidney disease. And it was a signal in that population that then led sponsors to say let's do a study only in that population. But they had a tremendous amount of information in the mild to moderate category even though that wasn't the intention of this study. The intention was just to take people with generally normal kidney function.

DR. TERZIC: Please?

DR. AWNI: Walid Awni, industry representative. Isn't that situation dependent? You already have 4 or 5 subjects with severe renal impairment. You have that data, and you're trying

to compare it to normal. You're trying to compare it to moderate. If the normal and moderate are receiving the same dosing adjustment and it was at the edge, you might want to go to -- if you compare it to moderate or renal, you're basically saying should I or shouldn't I adjust the dose?

So I'm not sure why the comparison -- it's a very small sample size. You do it all kind of different ways and actually make the best judgment call at that particular situation. I'm not sure -- needing to define a priori for all situations that must be this or that seems to be more restrictive relative to the data points that we are dealing with.

DR. TERZIC: Please?

DR. TENJARLA: I think my comment is very similar to Walid's comment. Essentially, you need to look at the richness of the data you have, and the sample size, and so on. So specific to the question what should be the reference group? Maybe one option is that you just go and look at your normal, and then if you have enough data points to

make a call on using the other one as a reference, you can try both, and then see which way is a better way of doing it. In the absence of that, with a very general question like that, the tendency is probably to go more towards normal only because you have the richness of data, and the data points, and a sample size.

DR. TERZIC: Thank you. Any other comments? Please?

DR. PAI: Again, I think for me -- this is Amit Pai, University of Michigan -- is the reference group is really kind of driven by the disease in question. So if you're developing a drug for Alzheimer's, for example, the normal might be in that 50 to 75 mL per minute range. So you want to make sure your dose is accurate for the majority of the population, and then some deviation from that for different degrees of renal function. So the way I see it, it's more the reference group is kind of defined by the disease that you're targeting.

DR. TERZIC: Any other questions? Please?

DR. SLUD: Back to the same question. It seems to me that the ultimate objective is to be estimating some quantity; for example, a dose multiplier, choosing a reference group that was, for example, smaller than it might be and analyzing just as a pairwise comparison with that group.

Why wouldn't you analyze jointly with all and make the best model that you have based on all, rather than just choosing another slice as a reference group and estimate the multiplier as best you can from the model; rather than choosing an intermediate response group or reference group at all?

DR. TERZIC: In summarizing so far what we have heard for this question, although there is a respect for introducing maybe a way not to have an all or none type of approach, it appears that the members of the committee pointed more to potential weaknesses or going away from the reference being really the normals.

The elements that they brought up include relatively limited numbers of information at this

point in terms of the depth of knowledge for groups outside of normal. The term of "noise" was introduced, which I think is pertinent here. Other terms were introduced such as the powering issues, which can be an issue potentially; terms like "prevalence" and the artificial almost cutoff may not really achieve what you're trying to achieve, and it may be more restrictive as somebody else mentioned it earlier.

I think the substantive aspect of all this is reminding that the reference should also be very much related to the targeted disease, and maybe in a way adjustable depending of the targeted disease. That's what we have heard; interesting.

DR. MORRIS: Andre, I think maybe the powering question was answered. I think I just misinterpreted the way the question was.

DR. TERZIC: Thank you. Any other comments for this question?

(No response.)

DR. TERZIC: If not, we will move to the last question of the day. It states, right now

there are multiple approaches for establishing an exposure match; in other words, matching based on point estimates, confidence interval based approaches, or exposure matching, 5th and 95th percentile, for example.

Here the FDA is very interested in the input in terms of how to select the best criteria for choosing one approach over another in this concept of exposure match. Please?

DR. AWNI: Walid Awni, industry representative. Honestly, in this question in particular, it's dying for data. If you have enough information, do it the old way and say, hey, if we use this criteria, this is better. Right now for me, if I pick any of these things -- and I have an opinion, but it's not based on information -- I would just say, oh, I probably would go with this.

For me, I'd love to have data to say we looked at 50 NDAs and the analysis of data. It's a good summer fellow or a graduate student's work and to say this is fantastic. When we look at all of these things, here is the decision, and therefore

we recommend this approach.

DR. TERZIC: Any other comments? Please?

DR. ZINEH: I was just going to follow up with just a clarification on the nature of the data, because in my mind, that sort of analysis requires a truth standard. What is the best approach? What would we be benchmarking?

I'm just trying to understand if we were going to go back and dig up more data that, let's say, compares the three different strategies, are you saying -- one way to look at it is does it matter? If you compare the three, do you end up with the same dosing recommendation? That's the only thing that I could think of that might be answerable, but are there other questions that this kind of analysis could help inform?

DR. COOK: I think we got the case recently for peds, and we're looking at a dosing recommendation there. I think the trough ratio changes a little bit because of the difference in clearance with a younger population.

The idea was we'd first try to match total

exposure, but we then looked at similarly what the distribution was, and we wanted to make sure that not a significant portion will exceed some concentration. So we actually ended up going with a lower dose than one might recommend because of the width of that. So we looked at the point, but it wasn't only on the point because of a safety concern. I don't know if that's helpful or not.

DR. TERZIC: Do we have maybe an unbiased approach to this question? Let's ask our statistician expert his opinion.

DR. SLUD: Eric Slud. It seems to me that you're interested in comparing bioavailability as measured by an entire curve, but you're simplifying to one of these approaches. If you had a way of adjusting to make the entire curve the same, that's what you would want to do.

If you've just adjusted it by, for example, an overall AUC or any of the other methods that you might use, you'd like to be able to judge, in a disease-specific way, the closeness of the curve that you've attained to the one that you're

desiring to attain. To be comparable to the bioavailability for the normals, you'd like to know how close it was. The measure of how close it was shouldn't be something that a statistician should answer, but a medical person, to say what was actually driving the response to the drug. It might be the overall area. You might have used an adjustment method, but then to see how successful it is, it's going to depend on how the shape of the curve relates to the response in the disease.

DR. TERZIC: Any other comments?

DR. MORRIS: Very quickly. Just so I have the question -- this is Ken Morris from Long Island University -- irrespective of which parameter of the AUC or Cmax, whatever it is that you're using, the goal is to have it be the same. So are you saying, Eric, that you can use a statistical method to determine if it's the same, but which parameter you use is a matter of more medical advice other than statistical?

DR. SLUD: I think it should certainly be medical. Just to be clear, supposed you used AUC

to do your adjustment, but it actually is a Cmax driven disease? You would want medical people to say, well, what was the effect of getting it wrong in that way?

DR. MORRIS: No, I agree. But I thought that the question from FDA was for whichever parameter you choose, whether or not it's a point confidence interval or clinical data, there should be agreement on which one to use or which combination.

DR. SLUD: To respond to it that way, if drugs for a particular disease were exactly driven by one of those methods, AUC, or Cmax, or whatever it was, then you just have to decide which it is. But probably it isn't like that. You're trying to get the curves overlay as well as you can, and if they did, then you'd say you had adjusted it completely. But to judge how inadequately you have brought them together is a medical question because it's not going to be any one of those specific parameters.

DR. COOK: I kind of bucket those in two,

the point estimate because so many chronically administered drugs, efficacy is driven by AUC or at least that's what we think. So should I match exposures because I know that matching AUC is likely to produce the same efficacy?

When you get into ranges, the question there is I probably don't want a significant portion of my group to be higher than something I have deemed might be at risk. So you're really asking should I be exposure matching on efficacy or should I be exposure matching on the risk of safety to try to keep a significant amount of people below a certain level while having their efficacy as close as possible there. I think that's what it is when you look at those upper limits.

You could flip it and say I want to make sure that I have at least the exposure of this in that population, so it could be also looked at efficacy I guess, but it's usually we're only looking at the upper range, more considering about safety, and that's how you kind of set your example. So that's what I'm reading into your

presentation.

DR. MADABUSHI: Sure. There are a couple of ways of thinking about it. Let's say that we are looking at results of a stand-alone renal impairment study. I think more often than not -- Dr. Awni also talked about it -- it just looks at the ratios, essentially. That's the point estimate. You could make it a bit fancier with the confidence intervals also.

But we also talked about utilizing totality of information to inform, whether it be for safety or whether it be for efficacy. One could, in a particular situation, say I do not want to be below a certain threshold because maybe these are anti-infectives because I don't want the risk loss of efficacy or having resistance [indiscernible], things of that nature.

So it depends upon which approach you use. Like you correctly pointed out, we are trying to address different aspects of it. On a fundamental level, one could argue these are all on an average adjusting for something, but we are talking about

utilizing either only the results of a stand-alone study and look at it in an isolation or use that to look at the clinical experience in general, or actually a conferred clinical experience that we have.

This is the range of situations, and that's where we are looking; should we try to come up with an approach that would take into account some of these good features that we thought we heard, and if so, how do we go about it, or are these automatically covered irrespective of whichever method we are here. That was the input that we are trying to seek.

DR. PAI: Amit Pai, University of Michigan. I know this is about renal impairment, but again, when we think about renal function, we think about the entire spectrum. I know there were points raised about calculation and different equations used for this. Clearly, there are biases with each of these equations, but the way by which we even categorize those failed. For example, MDRD does not allow you to estimate values above 60 mL per

minute. So we're using metrics to include people in these trials that can't be used across the entire spectrum.

Part of that is also when we're thinking about this exposure-match scenario where you have your reference group and your exposure matching, we keep thinking of it in a unidirectional way, so we're trying to reduce doses, but we're not thinking on the other side, which is the case with anti-infectives.

I think when we're thinking whatever is the right way -- and I'm not sure what the right way is -- we have to also be thinking about the other N, which is those with augmented kidney function, which is a phenomenon that happens.

DR. ZINEH: Just one kind of follow-up question. One of three scenarios we provide is matching to the range of exposures in clinical trials, and that would necessarily create -- it moves away from the categorical approach that we are sort of comfortable with. It moves towards almost developing a drug-specific cutpoint for

which you would be thinking about adjusting.

Does the committee see any concern, have any concerns with that approach? In other words, it's not your 30, 60, 90; it's now this drug is at 45 where you adjust; 70 is where you adjust. Does this represent a challenge in practice?

DR. NOLIN: I don't think it represents a challenge at all. Docs look at GFRs every day. I would argue that outside of type A pharmacists who are associated with these categorical cutpoints associated with drugs, most docs see it as a continuous measure, and whether or not the cutpoints are at 75 or 60 is irrelevant. So I think we should pursue the best approach. If there's only one categorical cutpoint at which a change should be made, we should make it at the appropriate level, irregardless of whether it matches with what the current kidney function category cutpoints are.

DR. NACHMAN: I actually want to go one step further. I think I would rather do it that way because those categories are arbitrary, and

some people do get stuck on I'm at 31 and not 29. So I think it makes perfect sense to do it the way you're suggesting.

DR. THADHANI: I guess the third person in line is going to concur with my predecessors here. The reason being is because a number of people have said this, and that is we have a wealth of information. Whether I like it or not, when I log in to the computer, I get the GFR. It's flashed in front of my face, and I can't get rid of it because my epic says I need to know about GFR, so that's exactly what Patrick highlighted.

We should celebrate the variation and the diversity, and that's obviously what Tom highlighted. But we have to remember that it's an inexact science. So even though you may decide that 75 is critical, understand that there's probably a 20 percent, 30 percent variation on that number. Hence, what you should do is exactly what my predecessors have said, which is just celebrate and understand the diversity.

DR. TENJARLA: Srini Tenjarla, industry

rep. I agree with the three comments made by the previous panelists, and I think it makes perfect sense from a scientific perspective. But also looking purely from the industry perspective, I think it's hard to move forward without knowing exactly where you stand early on in the game; otherwise, the rules of the games keep changing, which makes it very difficult, only because, whether we like it or not, it, the industry works in a certain way, where you have different people from different functions getting together. And changing the rules in the middle of the game makes it more difficult to have a clean path forward.

DR. NOLIN: I'll just make one more related comment. To my mind, the primary benefit of the traditional creatinine clearance or eGFR categories that are in the renal impairment guidance document relate to enrollment of subjects. I think it's important for the purposes of ensuring that we're enrolling subjects across the full spectrum of kidney disease, but I do not think that we should necessarily force ourselves to create dosing

recommendations in each of those categorical cutpoints. I don't think that the two are necessarily married to one another.

DR. COOK: The good news is, of course, we analyze the data that way when we're coming up with dosing recommendations. And what you're suggesting is not that much different, again, what we do with pediatrics, is there are not set weight distributions that we make dosing recommendations for. We figure out what we think are reasonable cutpoints, so it's easily doable.

DR. NACHMAN: I wanted to come back to the enrollment criteria issue. In real life, we do change that cutoff point based on the disease category and the disease characteristic on what we do know from the pharmacokinetics of an individual drug. So I don't think that we are currently stuck to certain points.

DR. FINESTONE: I'm going to say something again. I appreciate the fact that there are rules in place, and that there are parameters in place, and there are ranges in place, but I also applaud

the clinician's ability to make that decision on an individual basis. Every patient is an N of 1, one, and I can tell you that my husband is different every day, and it depends on when he comes into the clinic and how the clinician sees him and appreciates that difference.

So I applaud the fact that there are parameters, and I applaud the fact that there are exception to parameters.

DR. TERZIC: This was also an important discussion related to the last questions. I think we should actually start from the last point, and the last point re-emphasized the individuality of each patient. And each situation, which maybe renders your job more challenging, but it does reflect the reality of the patient substrate and the way to manage it.

I think some of the concepts you heard here range from ensuring that the enrollment does cover the spectrum of renal impairment. I think that was emphasized towards the end. That doesn't mean that those criteria are already preset and in stone.

They do evolve; that also we heard. So you will have to be very cognizant of this evolution of staging, let's say, disease. I think that was one point.

I think you can take it from the very first comment there is more data needed, but then you're saying there is enough, probably, data from the GFR, let's say, standpoint, and you're looking more for a daily solution.

I think the comment was very practical for, let's say, efficacy criteria. Looking for everything that is above sounds very reasonable as an approach, and for safety, everything that is below I think sounds also very reasonable.

So I don't know if you got a clear answer to your question, but I think the statistic by itself, as we heard, will not give you necessarily the solution, rather that each particular case should be looked at individually.

Any other comments?

(No response.)

DR. TERZIC: At this stage, typically what

we do, is we provide the opportunity to the FDA to ask their last comments since they have such a unique committee in front of them with diverse expertise; so if there is any last questions from the FDA towards the committee, any burning questions or any clarifications, or any closing statements as well?

DR. ZINEH: I would like to thank the committee, the chair, the Office of Clinical Pharmacology staff, the advisory committee staff, Dr. Graham, and the open comment speaker. This was a very rich conversation. It's given us a lot of specifics to go back and think through.

I guess the only thing that I would lay out there in addition to my thanks is some homework or a charge that maybe your work here is not done. One of the things that I'm struck with is this issue of the paradigm change. There's a little bit of a chicken and egg scenario.

If we were to signal our regulatory willingness to accept alternative paradigms, that's usually not enough. That does not address

regulatory uncertainty. Companies want to then know, well, what are you going to do with the information? So our experience with these alternative approaches is very limited.

One way to think about this is -- we have advisory committee members that come from many different sectors: academic, clinicians, researchers, pharmaceutical industry scientists -- how we might go back and stimulate more work to be done, and maybe even proof of concept, of the actual concepts that these designs raise in order to generate some more confidence or some more questions around these approaches. But I really want to thank everyone for their thoughtful contributions to the session.

Adjournment

DR. TERZIC: I would like also to echo, I believe, on the behalf of all the members around the table, the thankfulness we have towards the FDA of phrasing this particular question. I think your last comments on the paradigm shift and paradigm change is a pretty profound one, and I think all

the members are ready to assist the FDA, and other specific components of the FDA, with anything that needs to be done to ensure the best solutions are brought forward. So we look forward to the next opportunities with you.

They passed me something that probably I need to read more carefully, which is, very formally, we are adjourned now, so that's the first point. Another very important point is you need to leave your badges, as much as you may like them. But they will be recycled, so you should leave them at the table. Be careful to take all your personal belongings, otherwise they go into the museum at the FDA.

Again, thank you so very much. I think we need to thank also the audience that have been with us throughout these few hours. It was actually a very fantastic committee meeting, and thank you so much for having us.

(Whereupon, at 3:18 p.m., the meeting was adjourned.)