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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

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1 P R O C E E D I N G S

2 (8:30 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

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

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

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

1 pharmaceuticals from the University of Iowa.

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

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

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

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

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

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

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

22 DR. DOWLING: Good morning. Tom Dowling,

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

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

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

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

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

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

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

22 DR. SAHRE: Good morning. Martina Sahre,

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

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

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

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

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

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

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

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

1 pharmaceutical analysis.

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

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

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

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

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

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

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

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

21 **Conflict of Interest Statement**

22 DR. FAJICULAY: The Food and Drug

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 presentation and/or comments made by the speaker.

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

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

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

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

6 **FDA Introductory Remarks - Kellie Reynolds**

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

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

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

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

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

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

1 It's difficult to predict who will respond
2 to many treatments for chronic conditions. For
3 example, Brian Spear and colleagues surveyed
4 response rates for approved drugs in several major
5 disease areas and found wide ranges and responses,
6 depending on the area, but many were less than
7 50 percent.

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

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

22 In its current state, there's a tension in

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

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

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

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

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

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

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

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

11 Finally, there are multiple approaches for
12 establishing an exposure match. It can be matching
13 based on a point estimate, confidence interval
14 based approaches, exposure matching the 5th and
15 95th percentile, and there are others. Please
16 discuss the criteria for choosing one approach over
17 another.

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

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

5 That concludes my opening remarks.

6 Dr. Martina Sahre will now provide information
7 about the current paradigm for evaluating the
8 effect of renal impairment during drug development.

9 **FDA Presentation - Martina Sahre**

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

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

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

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

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

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

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

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

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

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

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

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

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

1 workshop, there was a presentation on renal related
2 exclusion criteria that one of our colleagues from
3 the FDA made, and they presented a retrospective
4 non-random sample of 38 clinical trials that was
5 assessed for exclusion criteria, and they found
6 that roughly 80 percent of these trials, of these
7 38 trials, had exclusion criteria related to renal
8 disease; 60 percent excluded based on creatinine
9 clearance or eGFR, and also based on serum
10 creatinine.

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

17 In a slightly more comprehensive analysis
18 of new molecular entity approvals that were from
19 2016 to 2017, colleagues in OCP assessed the
20 submission packages for these 67 new molecular
21 entities for their late-phase trials and the
22 exclusion-inclusion criteria in these late-phase

1 trials for renal related exclusion criteria.

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

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

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

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

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

20 The guidance states that that's the case
21 when you have a drug that is excreted up to
22 30 percent or more into urine as unchanged parent

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

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

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

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

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

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

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

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

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

8 So now that we have all this data, how does
9 that translate into the information content with
10 regard to how to dose these patients in labels?
11 What we did to understand how the data translates
12 to labels is we looked at approvals from the last
13 3 years of approval, from 2016 to 2018. There were
14 127 total approvals, and out of those, we looked at
15 a 115 labels; 33 of them were BLAs and 82 were
16 NDAs, and we parsed these labels for information
17 regarding dosing in patients with renal impairment.

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

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

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

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

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

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

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

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

1 that remain.

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

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

19 **FDA Presentation - Rajanikanth Madabushi**

20 DR. MADABUSHI: Good morning, everyone.

21 Thank, Dr. Sahre.

22 On the next few slides, I will set up the

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

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

22 An understanding of dose-exposure-response

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 We have observed this kind of phenomena for

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

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

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

1 is to achieve the same benefit-risk.

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

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

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

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

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

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

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

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

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

1 impairment, and what some of the concentrations
2 could be.

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

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

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

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

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

22 For example, this was the finding of a

1 stand-alone renal impairment study across the
2 categories of renal function, and the geometric
3 mean ratio is computed relative to the normal such
4 that here mild a 30 percent increase, moderate is
5 2-fold, and severe impairment has 4-fold increase.

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

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

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

9 So that line of would represents your
10 normal renal function, and the point estimate and
11 90 percent confidence intervals are computed for
12 each of the groups.

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

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

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

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

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

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

9 Based on the understanding of the
10 exposure-response relationships, and even the
11 benefit-risk understanding in this particular
12 situation, one could posit intervals almost similar
13 to the no-effect boundaries, but now this is on the
14 range. For example, I'm showing you here 5th and
15 95th percentiles of this particular experience as
16 being acceptable.

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

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

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

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

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

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

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

1 **Clarifying Questions to Presenters**

2 DR. TERZIC: Thank you very much.

3 Actually, thanks to all the speakers from the FDA
4 for very nicely presenting and framing the
5 questions. We do have some time for clarifying
6 questions, and this is important to the FDA as they
7 continue to work on this subject. So the floor is
8 open. Please recognize yourself and the
9 institution from where you come.

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

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

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

1 pharmacokinetic order?

2 DR. SAHRE: Yes.

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

10 DR. MORRIS: Thank you.

11 DR. COOK: Jack Cook, industrial
12 representative.

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

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

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

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

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

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

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

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

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

22 DR. TENJARLA: Srini Tenjarla, industry

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 DR. TERZIC: Dr. Thadhani?

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

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

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

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

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

1 practitioners, myself included.

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

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

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

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

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

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

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

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

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

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

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

20 But generally, we are looking at the
21 clinical experience that represents, I don't know,
22 2- to 3-fold of exclusions, wherein there were no

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

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

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

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

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

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

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

16 I'd like to hear your comments about that.

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

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

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

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

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

5 DR. TERZIC: Please?

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

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

22 This goes back to the question of

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

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

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

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

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

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

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

1 dedicated to the question of inclusion and
2 exclusion criteria.

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

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

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

1 30 percent renal eliminated drugs, or that's not
2 defined, that could be also for non-renal
3 eliminated drugs?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 Jay, go ahead.

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

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

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

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

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

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

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

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

9 DR. MADABUSHI: Yes --

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

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

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

1 or changing the dose based on the adjustment
2 factor?

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

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

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

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

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

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

22 DR. SLUD: Eric Slud, University of

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

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

16 Could you comment on that?

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

1 clinical experience would be available, and use all
2 of that to translate as opposed to having this
3 a priori assumption, which cannot be tested, but we
4 somehow have to believe that to be true.

5 Otherwise, there would be a gap in the labeling,
6 and there would be patients who might need dosing,
7 and there will be an uncertainty that could exist
8 with it.

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

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

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

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

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

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

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

1 will invite you more for a break. We'll take a
2 20-minute break and reconvene around 10 to 11.

3 Thank you.

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

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

11 **Presentation - Richard Graham**

12 DR. GRAHAM: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Just one slide on the dedicated PK study in

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

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

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

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

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

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

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

1 subsequent slides.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 The label is relatively silent with regard

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

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

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

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

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

9 Before I do that, though, I just wanted to
10 set the stage with some key highlights from a
11 poster that was presented in 2014 by Islam Younis.
12 In this poster, Islam noted that only 4 percent of
13 FDA-approved new molecular entities from 2000 to
14 2012 require dose adjustments in subjects with mild
15 renal impairment. The take home from this work was
16 that subjects with renal impairment should be
17 enrolled into late-stage studies using a risk based
18 approach, and that approach should be based upon
19 data that comes from the preclinical setting, as
20 well as early clinical data.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 This is not likely to be a

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

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

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

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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

1 would be great. And we can get started.

2 Shiew-Mei?

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

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

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

1 I think the other good point that you make
2 is to use all the available data. I think you have
3 shown us a slide where we may have only used one or
4 two -- powerful information. I think that's in
5 slide 9 or 10. I think that's a very good point.
6 I believe we really need to know our disposition
7 well in order for us to make -- okay, this is slide
8 10.

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

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

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

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

14 I think especially, you mentioned 0.8 to
15 1.25 or within 2-fold of the clinical observation.
16 I think that will -- I look forward to your paper,
17 but I was curious about do you have all that
18 information.

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

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

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

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

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

1 predictions are going to be relative to the
2 observations.

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

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

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

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

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

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

22 The other is that it fails to consider the

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

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

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

1 one piece of the puzzle.

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

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

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

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

1 DR. SUN: Both.

2 (Laughter.)

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

5 (Laughter.)

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

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

22 DR. NACHMAN: As a nephrologist and

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 and a real problem.

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

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

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

22 DR. COOK: This is a clarification comment,

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

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

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

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

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

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

13 DR. MORRIS: Thank you.

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

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

1 DR. BERINGER: Correct.

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

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

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

22 DR. ZINEH: Just seeking clarification on

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

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

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

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

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

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

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

21 (Whereupon, at 11:45 a.m., a lunch recess
22 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.

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

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

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

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

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

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

13 Thank you.

14 DR. CHOU: Thank you. I'm Ting-Chao Chou,
15 born in Taiwan, natural citizen, U.S. citizen in
16 1976. I received my PhD degree from Yale
17 University and pharmacology training at Johns
18 Hopkins University School of Medicine. I joined
19 Cornell University [indiscernible] professor, and I
20 work mainly at Memorial Sloan Kettering Cancer
21 Center in New York.

22 I retired from Sloan Kettering in 2013, and

1 I formed a company called PD Science, LLC, which I
2 have no conflict or any pharmaceutical product.

3 I'm mainly a theoretical pharmacologist.

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

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

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

22 The median-effect equation, as you can see,

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

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

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

17 It's a very general principle. Extension
18 of median-effect equation gives rise to
19 [indiscernible] effect equation. We have a paper
20 published in 1984. Just one article alone received
21 6,100 citations; 1,200 journals virtually cover
22 entire disciplines of biomedical sciences. In

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

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

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

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

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

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

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

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

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

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

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

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

16 When I say point, it's not number of
17 patients. It means the data for 1 dose and 1
18 point. With 1 point, you can have 5 patients,
19 10 patients, 100 patients. That's my theory.

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

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

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

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

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

4 So I present here, just that you know, a
5 very simple, easy way to streamline. If you keep
6 tracing the trivial and every variability, there's
7 no end of it. For example, in terms of a 2-drug
8 combination, it's very easy in vitro. I can do it
9 in 2 to 3 weeks. In animal, I can do it in 2 to
10 3 months. In clinical trial -- I'm not a
11 clinician, I'm a PhD -- it can be done. I have a
12 proposal actually presented at Johns Hopkins
13 University and other places, in Asia, too. So it
14 is so simple and fully automated.

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

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

1 what is synergy. Synergy is so important because
2 it's everywhere. Here, this is 10 plus
3 120 years -- 10 synergy if determination. Look at
4 it entirely, and my article, 4,800 citations. This
5 is the trend over the past 5 years. Look at other
6 methods. Many studies teach, and they miss the
7 point.

8 Drug combination --

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

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

15 **Questions to Committee and Discussion**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Also somebody said we do it for global

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 DR. MORRIS: Yes.

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

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

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

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

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

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

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

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

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

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

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

1 The second point I'll make is that we talk
2 about end-stage renal disease being different, and
3 there's no question end-stage renal disease, those
4 patients have differences between patients in stage
5 3 and 4.

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

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

1 in addition to multiple comorbidities.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 drug. To be consistent, as mentioned in
2 Dr. Reynolds' slides, right now our criteria is
3 that there's no dose reduction if it's known that
4 30 percent or less than 30 percent are excreted in
5 the urine.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 impairment.

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

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

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

21 Please?

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

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

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

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

1 2-fold increase in systemic exposure. It seems to
2 me that in these patients in whom there's already a
3 proposal to reduce the dose, that is an excellent
4 opportunity to embed in these trials some intensive
5 sampling to determine what the PK in corresponding
6 dosing requirements are to satisfy what we're
7 talking about here.

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

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

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

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

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

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

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

4 DR. TERZIC: One last question?

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

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

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

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

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

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

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

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

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

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

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

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

17 Shiew-Mei?

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

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

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

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

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

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

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

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

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

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

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

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

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

1 from the group.

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

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

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

17 DR. TERZIC: Dr. Collins?

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

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

8 DR. TERZIC: Please?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 Please?

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

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

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

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

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

21 Please?

22 DR. KRAFT: Walter Kraft, Jefferson. In

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

13 DR. THADHANI: I'll take a stab at what
14 Patrick started. Let me give you some concrete
15 examples. Recently in the nephrology community,
16 we've identified a genetic risk factor among
17 African Americans in terms of progression of kidney
18 disease; in this case, a particular genotype,
19 APOL1. When you look at those individuals with
20 2 copies of the variant, the acceleration of kidney
21 disease in that population is about 1 and a half to
22 2 times faster than comparable GFRs in the

1 Caucasian population without those 2 variants.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 There is one last comment. Please?

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

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

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

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

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

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

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

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

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

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

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

15 DR. TERZIC: Can you please speak more
16 closely?

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

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

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

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

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

1 I'll use an example to illustrate it.

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

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

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

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

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

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

5 (No response.)

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

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

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

1 studied and numerous makes the final results more
2 solid.

3 DR. TERZIC: Please?

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

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

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

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

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

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

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

21 Is that what you are saying?

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

1 question we are asking.

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

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

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

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

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

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

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

18 DR. TERZIC: Please?

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

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

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

15 DR. TERZIC: Please?

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

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

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

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

22 DR. TERZIC: Any other questions? Please?

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

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

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

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

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

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

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

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

20 (No response.)

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

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

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

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

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

1 we recommend this approach.

2 DR. TERZIC: Any other comments? Please?

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

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

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

22 The idea was we'd first try to match total

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

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

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

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

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

11 DR. TERZIC: Any other comments?

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

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

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

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

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

22 DR. COOK: I kind of bucket those in two,

1 the point estimate because so many chronically
2 administered drugs, efficacy is driven by AUC or at
3 least that's what we think. So should I match
4 exposures because I know that matching AUC is
5 likely to produce the same efficacy?

6 When you get into ranges, the question
7 there is I probably don't want a significant
8 portion of my group to be higher than something I
9 have deemed might be at risk. So you're really
10 asking should I be exposure matching on efficacy or
11 should I be exposure matching on the risk of safety
12 to try to keep a significant amount of people below
13 a certain level while having their efficacy as
14 close as possible there. I think that's what it is
15 when you look at those upper limits.

16 You could flip it and say I want to make
17 sure that I have at least the exposure of this in
18 that population, so it could be also looked at
19 efficacy I guess, but it's usually we're only
20 looking at the upper range, more considering about
21 safety, and that's how you kind of set your
22 example. So that's what I'm reading into your

1 presentation.

2 DR. MADABUSHI: Sure. There are a couple
3 of ways of thinking about it. Let's say that we
4 are looking at results of a stand-alone renal
5 impairment study. I think more often than
6 not -- Dr. Awni also talked about it -- it just
7 looks at the ratios, essentially. That's the point
8 estimate. You could make it a bit fancier with the
9 confidence intervals also.

10 But we also talked about utilizing totality
11 of information to inform, whether it be for safety
12 or whether it be for efficacy. One could, in a
13 particular situation, say I do not want to be below
14 a certain threshold because maybe these are
15 anti-infectives because I don't want the risk loss
16 of efficacy or having resistance [indiscernible],
17 things of that nature.

18 So it depends upon which approach you use.
19 Like you correctly pointed out, we are trying to
20 address different aspects of it. On a fundamental
21 level, one could argue these are all on an average
22 adjusting for something, but we are talking about

1 utilizing either only the results of a stand-alone
2 study and look at it in an isolation or use that to
3 look at the clinical experience in general, or
4 actually a conferred clinical experience that we
5 have.

6 This is the range of situations, and that's
7 where we are looking; should we try to come up with
8 an approach that would take into account some of
9 these good features that we thought we heard, and
10 if so, how do we go about it, or are these
11 automatically covered irrespective of whichever
12 method we are here. That was the input that we are
13 trying to seek.

14 DR. PAI: Amit Pai, University of Michigan.
15 I know this is about renal impairment, but again,
16 when we think about renal function, we think about
17 the entire spectrum. I know there were points
18 raised about calculation and different equations
19 used for this. Clearly, there are biases with each
20 of these equations, but the way by which we even
21 categorize those failed. For example, MDRD does
22 not allow you to estimate values above 60 mL per

1 minute. So we're using metrics to include people
2 in these trials that can't be used across the
3 entire spectrum.

4 Part of that is also when we're thinking
5 about this exposure-match scenario where you have
6 your reference group and your exposure matching, we
7 keep thinking of it in a unidirectional way, so
8 we're trying to reduce doses, but we're not
9 thinking on the other side, which is the case with
10 anti-infectives.

11 I think when we're thinking whatever is the
12 right way -- and I'm not sure what the right way
13 is -- we have to also be thinking about the other
14 N, which is those with augmented kidney function,
15 which is a phenomenon that happens.

16 DR. ZINEH: Just one kind of follow-up
17 question. One of three scenarios we provide is
18 matching to the range of exposures in clinical
19 trials, and that would necessarily create -- it
20 moves away from the categorical approach that we
21 are sort of comfortable with. It moves towards
22 almost developing a drug-specific cutpoint for

1 which you would be thinking about adjusting.

2 Does the committee see any concern, have
3 any concerns with that approach? In other words,
4 it's not your 30, 60, 90; it's now this drug is at
5 45 where you adjust; 70 is where you adjust. Does
6 this represent a challenge in practice?

7 DR. NOLIN: I don't think it represents a
8 challenge at all. Docs look at GFRs every day. I
9 would argue that outside of type A pharmacists who
10 are associated with these categorical cutpoints
11 associated with drugs, most docs see it as a
12 continuous measure, and whether or not the
13 cutpoints are at 75 or 60 is irrelevant. So I
14 think we should pursue the best approach. If
15 there's only one categorical cutpoint at which a
16 change should be made, we should make it at the
17 appropriate level, irregardless of whether it
18 matches with what the current kidney function
19 category cutpoints are.

20 DR. NACHMAN: I actually want to go one
21 step further. I think I would rather do it that
22 way because those categories are arbitrary, and

1 some people do get stuck on I'm at 31 and not 29.
2 So I think it makes perfect sense to do it the way
3 you're suggesting.

4 DR. THADHANI: I guess the third person in
5 line is going to concur with my predecessors here.
6 The reason being is because a number of people have
7 said this, and that is we have a wealth of
8 information. Whether I like it or not, when I log
9 in to the computer, I get the GFR. It's flashed in
10 front of my face, and I can't get rid of it because
11 my epic says I need to know about GFR, so that's
12 exactly what Patrick highlighted.

13 We should celebrate the variation and the
14 diversity, and that's obviously what Tom
15 highlighted. But we have to remember that it's an
16 inexact science. So even though you may decide
17 that 75 is critical, understand that there's
18 probably a 20 percent, 30 percent variation on that
19 number. Hence, what you should do is exactly what
20 my predecessors have said, which is just celebrate
21 and understand the diversity.

22 DR. TENJARLA: Srini Tenjarla, industry

1 rep. I agree with the three comments made by the
2 previous panelists, and I think it makes perfect
3 sense from a scientific perspective. But also
4 looking purely from the industry perspective, I
5 think it's hard to move forward without knowing
6 exactly where you stand early on in the game;
7 otherwise, the rules of the games keep changing,
8 which makes it very difficult, only because,
9 whether we like it or not, it, the industry works
10 in a certain way, where you have different people
11 from different functions getting together. And
12 changing the rules in the middle of the game makes
13 it more difficult to have a clean path forward.

14 DR. NOLIN: I'll just make one more related
15 comment. To my mind, the primary benefit of the
16 traditional creatinine clearance or eGFR categories
17 that are in the renal impairment guidance document
18 relate to enrollment of subjects. I think it's
19 important for the purposes of ensuring that we're
20 enrolling subjects across the full spectrum of
21 kidney disease, but I do not think that we should
22 necessarily force ourselves to create dosing

1 recommendations in each of those categorical
2 cutpoints. I don't think that the two are
3 necessarily married to one another.

4 DR. COOK: The good news is, of course, we
5 analyze the data that way when we're coming up with
6 dosing recommendations. And what you're suggesting
7 is not that much different, again, what we do with
8 pediatrics, is there are not set weight
9 distributions that we make dosing recommendations
10 for. We figure out what we think are reasonable
11 cutpoints, so it's easily doable.

12 DR. NACHMAN: I wanted to come back to the
13 enrollment criteria issue. In real life, we do
14 change that cutoff point based on the disease
15 category and the disease characteristic on what we
16 do know from the pharmacokinetics of an individual
17 drug. So I don't think that we are currently stuck
18 to certain points.

19 DR. FINESTONE: I'm going to say something
20 again. I appreciate the fact that there are rules
21 in place, and that there are parameters in place,
22 and there are ranges in place, but I also applaud

1 the clinician's ability to make that decision on an
2 individual basis. Every patient is an N of 1, one,
3 and I can tell you that my husband is different
4 every day, and it depends on when he comes into the
5 clinic and how the clinician sees him and
6 appreciates that difference.

7 So I applaud the fact that there are
8 parameters, and I applaud the fact that there are
9 exception to parameters.

10 DR. TERZIC: This was also an important
11 discussion related to the last questions. I think
12 we should actually start from the last point, and
13 the last point re-emphasized the individuality of
14 each patient. And each situation, which maybe
15 renders your job more challenging, but it does
16 reflect the reality of the patient substrate and
17 the way to manage it.

18 I think some of the concepts you heard here
19 range from ensuring that the enrollment does cover
20 the spectrum of renal impairment. I think that was
21 emphasized towards the end. That doesn't mean that
22 those criteria are already preset and in stone.

1 They do evolve; that also we heard. So you will
2 have to be very cognizant of this evolution of
3 staging, let's say, disease. I think that was one
4 point.

5 I think you can take it from the very first
6 comment there is more data needed, but then you're
7 saying there is enough, probably, data from the
8 GFR, let's say, standpoint, and you're looking more
9 for a daily solution.

10 I think the comment was very practical for,
11 let's say, efficacy criteria. Looking for
12 everything that is above sounds very reasonable as
13 an approach, and for safety, everything that is
14 below I think sounds also very reasonable.

15 So I don't know if you got a clear answer
16 to your question, but I think the statistic by
17 itself, as we heard, will not give you necessarily
18 the solution, rather that each particular case
19 should be looked at individually.

20 Any other comments?

21 (No response.)

22 DR. TERZIC: At this stage, typically what

1 we do, is we provide the opportunity to the FDA to
2 ask their last comments since they have such a
3 unique committee in front of them with diverse
4 expertise; so if there is any last questions from
5 the FDA towards the committee, any burning
6 questions or any clarifications, or any closing
7 statements as well?

8 DR. ZINEH: I would like to thank the
9 committee, the chair, the Office of Clinical
10 Pharmacology staff, the advisory committee staff,
11 Dr. Graham, and the open comment speaker. This was
12 a very rich conversation. It's given us a lot of
13 specifics to go back and think through.

14 I guess the only thing that I would lay out
15 there in addition to my thanks is some homework or
16 a charge that maybe your work here is not done.
17 One of the things that I'm struck with is this
18 issue of the paradigm change. There's a little bit
19 of a chicken and egg scenario.

20 If we were to signal our regulatory
21 willingness to accept alternative paradigms, that's
22 usually not enough. That does not address

1 regulatory uncertainty. Companies want to then
2 know, well, what are you going to do with the
3 information? So our experience with these
4 alternative approaches is very limited.

5 One way to think about this is -- we have
6 advisory committee members that come from many
7 different sectors: academic, clinicians,
8 researchers, pharmaceutical industry
9 scientists -- how we might go back and stimulate
10 more work to be done, and maybe even proof of
11 concept, of the actual concepts that these designs
12 raise in order to generate some more confidence or
13 some more questions around these approaches. But I
14 really want to thank everyone for their thoughtful
15 contributions to the session.

16 **Adjournment**

17 DR. TERZIC: I would like also to echo, I
18 believe, on the behalf of all the members around
19 the table, the thankfulness we have towards the FDA
20 of phrasing this particular question. I think your
21 last comments on the paradigm shift and paradigm
22 change is a pretty profound one, and I think all

1 the members are ready to assist the FDA, and other
2 specific components of the FDA, with anything that
3 needs to be done to ensure the best solutions are
4 brought forward. So we look forward to the next
5 opportunities with you.

6 They passed me something that probably I
7 need to read more carefully, which is, very
8 formally, we are adjourned now, so that's the first
9 point. Another very important point is you need to
10 leave your badges, as much as you may like them.
11 But they will be recycled, so you should leave them
12 at the table. Be careful to take all your personal
13 belongings, otherwise they go into the museum at
14 the FDA.

15 Again, thank you so very much. I think we
16 need to thank also the audience that have been with
17 us throughout these few hours. It was actually a
18 very fantastic committee meeting, and thank you so
19 much for having us.

20 (Whereupon, at 3:18 p.m., the meeting was
21 adjourned.)
22