FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY (PSCP) ADVISORY COMMITTEE

Thursday, September 20, 2018

12:32 p.m. to 3:33 p.m.

Afternoon Session

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(12:32 p.m.)

DR. AMIDON: Good afternoon. I'd first like to remind everyone to please silence your cell phones, and smartphones, and any other devices if you haven't already done so. I'd also like a to identify the FDA press contact, Jeremy Kahn. Jeremy, if you're present, would you stand?

My name is Gregory Amidon, and I am the chair of the Pharmaceutical Sciences and Clinical Pharmacology Advisory Committee, and I will now call the afternoon session of the meeting of the Pharmaceutical Sciences and Clinical Pharmacology Advisory Committee to order.

I'll start at this point by going around the table and asking each of you to introduce yourselves for the record, and I'm going to start on my right again with Dr. Awni, and we'll carry on. Thank you.

DR. AWNI: Walid Awni. I'm an industry representative. I work for AbbVie.

DR. COOK: Jack Cook, Pfizer, industrial

representative.

DR. TENJARLA: Srini Tenjarla, Shire Pharmaceuticals, industry rep.

DR. DONOVAN: Maureen Donovan, University of Iowa.

DR. SUN: Duxin Sun, University of Michigan.

DR. LI: Tonglei Li, professor of pharmaceutical sciences, Purdue University.

DR. FINESTONE: Sandra Finestone, consumer representative.

DR. MAGER: Don Mager, professor of pharmaceutical sciences, the University of Buffalo.

DR. AMIDON: Greg Amidon, professor at the University of Michigan.

CDR SHEPHERD: Jennifer shepherd, designated federal officer.

DR. CARRICO: Jeff Carrico, NIH.

DR. TERZIC: Andre Terzic, Mayo Clinic.

DR. SLATTUM: Patty Slattum, Virginia Commonwealth University.

DR. SMITH: Paul Smith, University of Maryland, College Park.

DR. POLLI: James Polli, University of Maryland, Baltimore.

DR. YU: Lawrence Yu, deputy director, Office of Pharmaceutical Quality, CDER, FDA.

DR. KOPCHA: Mike Kopcha, director of Office of Pharmaceutical Quality, CDER, FDA.

DR. AMIDON: Thank you.

For topics such as those that we're going to discuss this afternoon, there are a variety of opinions, some of which are very strongly held. Our goal, again, today is to be a fair and open forum for discussion of these issues, and the individuals can express their views without interruption. So just as a gentle reminder, individuals will be allowed to speak into the record only if they're recognized by the chair. And of course, we look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic

at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during the breaks this afternoon. So thank you with that

I'll now turn this over to Lieutenant Commander Jennifer Shepherd, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

CDR SHEPHERD: Good afternoon. The Food and Drug Administration is convening today's meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and

are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC, Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

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

Today, the committee will focus on two topics related to the Office of Pharmaceutical Quality's priority of promoting the availability of better medicine. For this afternoon's agenda, the committee will discuss in vitro/in vivo relationship standards and will seek input on establishing patient-focused dissolution standards for oral solid modified-release dosage forms.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial

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

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

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need

to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topic that could be affected by the committee's discussions. Thank you.

DR. AMIDON: Thank you.

We'll now proceed to the FDA presentations beginning with Dr. Lostritto.

FDA Presentation - Richard Lostritto

DR. LOSTRITTO: Good afternoon, everybody. I hope you had a nice, enjoyable lunch. I'm kicking off the session with three speakers today, this afternoon, and here's a little outline of the three talks you will have this afternoon.

I'll be talking about patient-focused quality dissolution standards for high solubility drugs and advances in predictive dissolution technology, the former being related to a guidance we recently published in the letter related to some other findings. Paul Seo will be talking about establishing the in vitro/ in vivo link for

pharmaceutical manufacturing quality, and Lawrence Yu will be talking about the understanding of bioperformance risk for extended-release, solid oral drug products.

Patient-focused quality standards, we can define them as a set of criteria and acceptance ranges to which drug products should conform in order to deliver the therapeutic benefit as in the label. It's two parts to that. So what we're trying to do is come up with an in vitro way to test to assure that the performance in vivo will be there.

Patient-focused quality standards can increase flexibility within the pharmaceutical manufacturing sector while maintaining quality by establishing acceptance criteria based on clinical performance instead of process capability or manufacturing process control. And that's important because the dissolution method often serves those purposes as well for QC and so forth, but we try to have it balanced so that it represents what's happening in vivo.

Patient-focused quality standards avoid under- or over-discriminating methods and specifications, both of which are contrary to patient needs. So in other words, you try to avoid a dissolution method that shows a very big response to a small change when in vivo that doesn't occur, or vice versa, when it doesn't show a change in vitro, and a very big change occurs in vivo.

First, I'll talk a little about a recently published guidance in August of this year on dissolution testing and acceptance criteria for immediate-release solid oral dosage form drug products containing high solubility drugs substances, a nice catchy title. On the right side, we shoot right to the bottom line -- and we'll talk more about it -- for high solubility drugs such as you see in BCS class 1 and 3, a single-point dissolution specification of Q 80 percent in 30 minutes; in other words, at least 80 percent dissolved in 30 minutes under certain conditions.

What are the eligible drug products? Well,

first of all, we're talking about immediate release, oral solid dosage forms meant to be swallowed, such as tablets and capsules that contain highly soluble drug substances. So what's highly soluble?

Well, to be considered highly soluble, the highest drug product strength should be soluble in 250 mLs or less of aqueous media over the pH range of 1 to 6.8 at 37 degrees, inclusive of those pH ranges. In other words, the highest strength divided by 250 should be less than or equal to the lowest solubility over the entire pH range of 1 to 6.8

Now in cases, in the guidance, it discusses where the highest dose in the label is more than the highest strength. That is an area of discussion with the agency.

Chewable tablets are within the scope of this guidance if dissolution studies are conducted on the whole tablet. They can be within the scope; don't have to be. Orally disintegrating tablets, or ODTs, may be within scope if it's shown that

there is no significant absorption from the oral cavity, the disintegration requirements for ODTs remain, and all the other criteria are met.

Sublingual and other dosage forms intended for absorption from the local action within the oral cavity are out of the scope of the guidance.

There are other considerations as well. The guidance does not apply to narrow therapeutic index drugs or NTI drug products because it's a critical relationship between bioavailability, efficacy, and safety, and a very narrow band between effective and toxic dose. If the time to maximum plasma concentration is critical for the intended use, the guidance doesn't apply. For example, rescue medications, rapid analgesia, and so on is out of scope of the guidance.

There are manufacturing considerations as well. So we want to make sure that the manufacturing and testing history of the drug product on stability are able to meet these dissolution criteria, so demonstrating the drug product meets the acceptance criteria and the

guidance under the standard testing conditions throughout expiry.

Also, the excipients have to be consistent in type and amount with the design of an immediate-release drug product. Certain excipients are used primarily to slow down the release rate from the tablet and so forth, or to delay it, and their use would put that product outside the scope of the guidance. Although it seems like there's a lot of things outside the scope, there are a lot of things within them as well.

Here is a summary of the standard dissolution testing conditions. The basket method, USP apparatus 1, standard conditions of 100 revolutions per minute stirring; 500 mLs of 0.1 normal HCl in the aqueous media; no surfactant in the media; and 37 degrees, a standard situation.

Likewise, for the paddle method, apparatus 2, a stirring rate of 50; 75 can be justified. If that's justified appropriately, then that condition may be allowed. You should discuss that with the agency. 500 mL of 0.1 normal HCl in

the aqueous media; again, no surfactant.

The information on the number of units to test and the overall method design, that's in the USP chapter 711 on dissolution. It is acceptable to add a few turns of a wire helix for capsules that may want to float so that they remain fully immersed in the dissolution media. If 900 mL, which is the capacity, is used, that should be justified. That's a fairly large volume if we're trying to become anything near something biorelevant.

Besides the recommended 0.1 normal HCl and aqueous media, other dissolution media within the physiological pH range may be acceptable if appropriate justification is provided. When we say appropriate justification, these can be discussed with the agency beforehand.

Here's the acceptance criteria as I mentioned up front for this guidance. The dissolution acceptance criteria is at least 80 percent dissolved in 30 minutes. And if an alternate acceptance criterion is proposed, also

the applicant should provide data to support that.

That was based on a relatively low risk of immediate-release, highly soluble drug substances in oral drug products. Traditional dissolution approaches are adequate for this low-risk situation. And I don't know why the number 3 appears there with all the eyes that looked at these slides. It should just say BCS class 1 and immediate-release drug products.

Patient-focused quality dissolution standards are established for these lower risk products by this guidance, and advances in predictive dissolution methodology and modeling may enable patient-focused quality dissolution standards for other classes and types of drug products, and that's what we're going to move into next in this discussion.

So dissolution studies go back to the 1960's, and most of the things that I will talk about in terms of summary of the current state, you can find corollaries or evidence for methodologically going back almost that far. So

why are they current? Well, work is continuing in these areas in novel ways using more sophisticated technology and more sophisticated computer modeling and so forth. So while it looks like some of the same, there are some new results, some surprising and some new directions being pointed to.

Let's go back to initial NDA approval. That's where you link dissolution performance of the clinical trial batches to clinical safety and efficacy. You don't have a lot of product history at the time, and that's usually where dissolution is linked to.

For example, in a quality-by-design scenario, where you study the influence of changes and your formulation and your process on the performance of the product, in that scenario, the robustness of dissolution behavior to small changes encountered during manufacturing and over shelf life are known. In other words, the dissolution model used at that time may be able to detect or respond to manufacturing or ingredient quality changes and so forth that could impact product

performance. That would be one of the goals.

However, usually in initial product approval, a causative and quantitative link of dissolution behavior to absorption and safety and efficacy is often not fully know or even absent. Why is that? Well, there are lots of things in play in addition to the drug development process. The anatomy and the physiology of the GI tract are not fully mimicable by any dissolution method. And the logical tendency is to choose the method that best suits your needs. If you're doing an immediate-release formulation of the capsule, you may choose one type of method. If you're doing a large tablet with a matrix extended release, you may choose another type of method, and so forth.

Also BCS class 2 and 4 drugs, which are poorly soluble drugs, are in general more problematic to deal with. And we'll talk about why that is. But in general, it's a solubility limited problem and dissolution limited problem.

Also, modified-release products, one of the things we're here to talk about today, are

inherently more complex. You have structures to the dosage form, which may be involved in limiting or controlling the release of drug. And there are different ways that that can happen. It can be continuous, and pulsatile, and so forth. It's an inherently more complex beast.

In vitro/in vivo correlations and relationships, development, they're very data laden, resource intensive, and albeit, increasingly aided by technological improvements in software and so forth. It can take a lot of time and resources to develop IVIVR and IVIVC.

Let's look at some of the contemporary areas of interest. We'll start with more biorelevant in vitro approaches. Simulated fluids to better mimic in a facile and feasible way, the fasted and fed fluids in the stomach, small intestine and the colon, which is a fairly complex milieu of a fluid; the use of USP apparatus 3 and 4 or others to simulate the changing GI environment that flow through cells and so forth -- again, they don't mimic much of the GI system -- or more complex

gastrointestinal simulators.

So these are more complex test systems to simulate the dynamic physiological processes within the GI tract, and they're usually multi-compartment systems to study dissolution. And one example is a two-phase dissolution system, which I'll show you a little bit more about artificial digestive systems, and so forth. You'll see an example of that. They're rather complicated and perhaps not feasible for so-called everyday or QC use.

Other more biorelevant in vitro approaches are informed by an increasing understanding of the intraluminal processes, what's going on near the sites of absorption. Also, inter- and intrasubject variability, how our bodies change with respect to GI function throughout the day, functional disease state within our own body, and between individuals, so inter- and intra variability. It's a big factor which decreases the granularity of dissolution related to absorption and so forth. It makes it more complicated.

Now, there have been some advances in

computational methods in a couple different areas. One is in computational fluid dynamics. This would be the area that studies what's happening in the liquid media adjacent to the solid dosage form, adjacent to the container that can affect or impact the rate of dissolution. There are also computational methods of a different type to study local processes underlying dissolution transport and absorption within the intestines, including PBPK or physiologically based pharmacokinetic based in silico frameworks. So those are your basic areas where you see a lot of activity.

The outcome of these studies may reduce and simplify all drug product testing while significantly reducing regulatory requirements. That probably should be a goal statement, but that would be a desirable outcome.

Aspiration and motility studies in healthy volunteers, these are the main population of bioequivalence or BE studies, looking at the GI and plasma concentration. These aspiration studies are semi-invasive, but you're measuring directly in

there, the intubation.

In this one example, the researchers looked at the GI and plasma concentrations of ibuprofen, which is a weakly [ph] acidic drug, and after oral administration, they used immediate-release ibuprofen tablets, USP 800 milligrams, and they measured various fluid compartments over time, including the plasma. They had a surprising finding of high levels of ibuprofen in the stomach and small intestine 7 hours post-dosing. And that was unexpected because you wouldn't have expected it to be still in those fluids at that time.

Their determination -- and this is 2017 -- is that future work is needed to better understand the role of various GI parameters such as motility, moving along the GI tract, which that actually goes back and forth with a net movement forth; gastric emptying, which again is not a consistent or time thing, and there are various factors that affect gastric emptying, the volume and so forth; and all these effects on systemic ibuprofen levels in order to improve the in vitro

predictive model. You're trying to predict from in vitro what's happening in vivo.

Magnetic resonance imaging is noninvasive. This is an MRI image taken of the individual while they are undergoing absorption in normal GI tract function. Additional insights into the contractile events or the motility events along the GI tract are going to be explored this coming year using MRI studies. It's kind of exciting because, like I said, it's noninvasive. You get a more natural view of what's going on. It's being used to quantify the time courses of the volumes of freely mobile fluid in the stomach, small intestine, the bowel, et cetera, and correlate that GI motility.

The current work is cross validating MRI small bowel motility protocol with one used previously at the University of Michigan. And the aim is to show that invasive methods can be better replaced by noninvasive MRI methods. And that actually is something that is novel and feasible as well. So that's going to be some interesting work to follow.

Here are some examples. This is a gastrointestinal simulator. I just show the pictures to see that, first of all, it is rather complicated, a series of beakers and pumps and so forth in a temperature-controlled bath, which can be controlled in terms of flow rate and time and so forth. But it doesn't really look much like anything inside the human body. So just looking at it, it's going to have some limitations. But it is an attempt to approximate various GI functions.

In other work similar to this, polydimethylsiloxane, or silicone membranes, were used successfully to mimic the GI absorption process, so that was interesting as well.

Here's an example of how computational fluid dynamics can be used. And you can see, starting from left to right, the sheer profiles that are imaged and the color of the image showing you the type of sheer profile going on, turbulent, laminar, convective, and so on. This gives a better view of what's happening inside the dissolution vessel.

At first, that may seem rather

straightforward because if you look at the image on the far right, that's your USP apparatus, vessel, too, but you can see from looking at the images that the hydrodynamics are far from uniform and not very straightforward in terms of -- it would be very difficult to do this without computational methods.

So they provide a window as to what is the in vitro device doing? How is that behaving? If we're going to be able to try and correlate that to what's happening in the human body, we have to certainly understand what's happening here in any in vitro system. So this is an important step to understanding that.

We've all heard the scene about the problems with a tablet that settles in a particular spot in the vessel, and it behaves differently than the adjacent vessel where tablets settle a little bit differently, and so on. This is an attempt to understand that and hopefully lead to more uniform or controllable hydrodynamics.

This is a two-phase dissolution system.

Here, you have an oil phase floating on top of an aqueous phase, and the aqueous phase is in that light blue color at the bottom in this one vessel. Both of those phases are stirred, and they can be stirred and sampled independently. So you can have two different stirring rates. They can even be stirred in opposite directions in some cases, and you can sample from either compartment.

In the aqueous phase, you can control the volume, the pH, the tenacity to tonicity, et cetera. And likewise, you can control the species of the oil used, the volume, the geometry of the interface, and so on. So it's quite a variable system. And why would somebody want to use something like this? It's obviously more complicated than a single-phase media.

Well, some of the pros are that the oil layer on top provides a sink for hydrophobic or low-solubility drugs, and poor solubility plagues dissolution methodology development. Usually people resort to surfactants. There are a few things less physiologically relevant than that.

So this is a way of providing a hydrophobic sink or a mechanism, or a way to -- I should say not a mechanism, but a means to estimate absorption by having an oil layer represent the lumen. But it certainly can provide a sink. It's relatively low tech, and if you judiciously choose the oil phase, and it's amount, and so forth, you may be able to mimic or estimate oral absorption.

Now, what are some of the cons against it? Well, it's far from standardized. And I think in that respect, it's a victim of its own flexibility as an approach. Every single paper seems to use a different type of approach to address this problem. There is a substantive use of organic solvents in most cases. In some cases, there are low-volume systems that show some promise, but that's not as green as we would like.

In situ media changes are cumbersome. If you want to be able to change the media during the course of dissolution run, it's more complicated in this system compared to a single-phase system.

Here's an example. Three different

apparatus variations were looked at by this researcher. They used multiple-phase volumes from 152 to 50 mL. They tried different stirring rates of the two different phases, different pH ranges, and so forth. The drugs they looked at, they tried multiple strengths.

They were able to actually correlate their in vitro results to reflect in vivo absorption kinetics. So in that particular study, by researching out what of these factors may have been important, they were able to at least get a rank ordering. By scaling, I mean rank ordering. They weren't saying if you got this rate of dissolution, you were getting that rate of absorption. No. They were saying there were rank ordering formulations in vitro that correlated with absorption in vivo.

In summary, predictive dissolution outcomes will more likely succeed through novel and multidisciplinary and collaborative approaches. You have the computational approach with fluid dynamics and PBPK, the in vitro approach with

gastrointestinal simulators, two-phase systems and others, and in vivo approaches, noninvasive in vivo approaches, where we're looking at the physiology of absorption more closely through magnetic resonance imaging.

That is it for me. Paul, you're up.

Thank you very much. I appreciate your attention.

FDA Presentation - Paul Seo

DR. SEO: Good afternoon. My name is Paul Seo. I'm the director of the Division of Biopharmaceutics in the Office of New Drug Products. First off, I'd like to thank the committee for convening today to provide guidance on the topic of in vitro/ in vivo, the link in the arena of quality.

In the Division of Biopharmaceutics, we're responsible primarily for new drug and generic drug assessment with regards to dissolution testing. And I'm here to provide you a high-level overview of where we've been, where we're currently are, and where we're attempting to go. And hopefully that

provides some information for you to help the discussions move along.

Rick mentioned this a little bit, and I'd like to dovetail onto that, which is patient-focused quality standards. To define it, patient-focused quality standards ensures that the delivery of the intended dose of drug to the site of action -- or is it available to the physiological system that is the patient, to ensure consistent safety and efficacy for the marketed product relative to those achieved by the clinical trial formulation.

Or put it another way, we are ensuring that the product that makes it on the market, that makes it on the shelf, is essentially the same as the product that underwent clinical trials and all the robust testing during development, precisely what Mike had mentioned this morning with regards to ensuring the quality of the next dose.

This is signified by test methods and acceptance criteria that are able to identify and reject drug product batches that are likely to

perform inadequately. What we're talking about is bioequivalence, and ultimately that's the goal of quality specification.

That being said, one of the primary test that we use in the quality arena is the dissolution test, which as you can tell, again, by the presentation that Rick just gave, dissolution testing is a relatively straightforward test, it's easy to understand, and that's one of the strengths, and that it's very well characterized.

I like to refer to it as the little engine that could, primarily because of the straightforwardness, but we ask a lot of the test. It's used in a variety of areas, both in pharmaceutical development, perhaps the stability studies and sending expiry dates, biowaivers related to both within a product line for different strengths or even scale-up and post-approval changes.

Interchangeability evaluation, which is a big deal, especially in the generics arena, routine QC testing to see if your process is under control

and for batch release. It's also used for a variety of dosage forms, solid orals, whether it be tablet, capsules, or powders, as well as inserts and implants and suspensions and what have you.

We're talking a lot about in vitro/in vivo relationships, but one of the primary ways that we link the in vitro data to the in vivo data is through IVIVC or in vivo/in vitro correlations. IVIVC in a nutshell, the objective of IVIVC is to establish a predictive mathematical model to describe the relationship between an in vitro property and in vivo response.

Primarily for the agency, what that boils down to is in vitro data, the dissolution test being typically what we see, being mathematically correlated to PK data. And both of these are actually surrogates to safety and efficacy.

The reason why IVIVC is important, and we've actually at the agency have been recommending it for so long, is because in vitro release tests could actually replace the needs for in vivo PK data; that is biowaivers. This actually, from an

ethical standpoint, minimizes the need for unnecessary human testing. It decreases the regulatory burden because once the IVIVC is validated and approved, it's a much easier thing to consistently look at in vitro data versus looking at a new PK study. This maximizes both regulatory and industry flexibility. For example, it allows many times for wider specifications to keep the product on the shelf.

So the IVIVC guidance is now approximately slightly more than 20 years old. It's been around since '97, and we have recommended its use for that amount of time. At the time the guidance was developed, it was based on sound science. And after doing an internal assessment, since 2008, the agency has received approximately 58 IVIVCs. And I'm only speaking in the new drug innovator space. There are a handful of IVIVCs also that have been received in the generic, although not quite as much. Within those IVIVCs, most of them have been for solid oral dosage forms at around 74 percent.

So the question really arises, why don't we

see more IVIVCs? It's important, it's relevant, but over the last 20 years, 50 some odd IVIVCs isn't a lot. It's possibly due to the fact that IVIVC is often seen as difficult. There are low acceptance rates. Out of those that the agency received, approximately 40 percent were found acceptable, and the other 60 percent were not acceptable or rejected.

From an industry perspective, from what I hear, there are resource barriers both in knowledge, cost, and time. And of course, there are the ethical considerations of why put undue necessary human studies when you don't have to, especially if you have all that clinical data up front?

Last but not least, IVIVC is often seen as an all or nothing approach. You put all this investment forward, but at the end of the day, if it's not approved, all of those resources are now wasted. There's no way to really salvage it.

Some of the common reasons that we've seen IVIVCs be unsuccessful are that the traditional

dissolution methods that they used to develop the model were not sensitive; that is, there may actually be a need for the dissolution test to be slightly more physiologically relevant. A lot of times, the dissolution tests that are received in IVIVCs are very straightforward, 900 mL, apparatus to vessel, that kind of thing.

Also, formulation variants don't always provide adequate change in release profile. They're just too similar. It's evident by the F2 [ph] profile, which is a metric to compare profiles to see how close they are. Sometimes the formulation variants that are submitted, they're not appropriate. For example, there are entire substitutions or release-controlling excipients, and that invalidates the model.

One of the things we also see is there's a lack of a priori planning of the IVIVC. A lot of times, the most successful cases are those cases where we've seen where the company or the sponsor has created and planned for the IVIVC up front. They've planned around those clinical studies, and

planned around those formulation variants, and incorporated that into their phase 1-2-3 trials. For those that have been unsuccessful, it's because from what we see, the data is, some of it's there, and they try to piece something together to try to attempt an IVIVC.

In the biopharmaceutics discipline, how are we going about establishing in vitro/in vivo relationships if IVIVC aren't really performing and we're not accepting them at this reasonable rate? Well, we are leveraging the clinical data that we already have, and we also have the in vitro data as part of that reassessment.

Sometimes that link is made through an IVIVC, but often times than not, what we don't receive is computational modeling. And that's the piece that is missing, at least from our discipline perspective, and that's what we're really moving towards and attempting in many of the new drug and generic drug arena.

With this emphasis on in silico modeling, I think it's important to understand that, really,

modeling is a tool. And there's a saying in the modeling world, "fit for use or fit for purpose." You have to define the problem and kind of work backwards.

So it's not particular to pharmaceutics or pharmaceutical R&D. The modeling is used in engineering, physics, quantum mechanics, entertainment arena, and what have you. But really what it boils down to is a simplification of the process where you distill down the most interesting or most relevant parameters, and you try to model that using a set of criteria, typically mathematical equations. You use the computer to take those mathematical equations and get an output, visualize it, validate and verify, and then you kind of go in a circle and you reassess and refine.

So based on that, there's something called, that we've been referring to today, physiologically based pharmacokinetic modeling or PBPK for short. PBPK is a mathematical framework of differential equations describing the anatomical compartments,

for example, the organs and tissues. And it's not unlike PKPD modeling, which many of you are probably already familiar with. But the main difference in PBPK is that it takes more of a mechanistic approach and parameterizes many of the different variables, and incorporates that into the model.

Conceptually, PBPK has been around for quite some time, since the late '60s, early '70s. But only recently has it really gained traction, at least at the agency, due to the technological advancements both from a CPU kind of processing power standpoint, but also due to the fact that there is commercially available software, and that really empowers many different companies and users.

The interesting thing about PBPK in general, and perhaps why we've seen such an uptick in its interest, is it aligns with PDUFA 7 with regards to MIDD or advancing model-informed drug development. PBPK has a variety of uses and purposes, and those vary depending on the office or area you're looking at within the agency. The Office of Clinical

Pharmacology uses it, the Office of Generic Drug uses it, and now the Office of Pharmaceutical Quality uses it specifically in the biopharmaceutics area. Again, we use it for a variety of means, but we have started to share the knowledge base and experience we've each gained and starting to collaborate to make for a better model.

So PBPK in biopharmaceutics, or what we've coined PBBP because of the specific use of PBPK for quality parameters, it's a risk-based approach where we leverage the risk to the patient, the total knowledge base of the data and totality to determine whether the PBBP is acceptable or not.

Typically, what we see is for the lower-risk products, the models have been found successful. Lower risk is generally where we have a larger data set and a larger understanding of the process of the substance or more straightforward parameters such as particle size or batch-release acceptance criteria.

The higher risk models generally involve a larger set of more unknowns and has a larger impact

because the model may be more pivotal; for example, a fallen biowaiver related to a SUPAC level change or something of that nature.

So far, since 2009, we have 29 NDA submissions involving PBPK to support biopharmaceutics. They have been increasing, but limited numbers of ANDAs are also submitting this information as well. Of the 29 NDA submissions that we looked at, 75 percent of the PBBP models were found acceptable from the discipline perspective. The takeaway there is 75 percent is a dramatic difference versus the 40 percent of acceptance rate for an IVIVC. And it's important to note that those models were actually added as supportive data to make the biopharmaceutics assessment.

Some of the use cases of PBPK in general throughout the agency, again, depending on the area, whether it's clin-pharm and generics or biopharm. We've seen it used for effect of food; effect of gastric pH; BCS classification; supporting data; special population assessment;

general risk assessment; IVIVRs; particle size distribution setting; and the most frequent use in the biopharm arena would be the dissolution method or acceptance criteria justification.

So drilling down to some specific case examples, with regards to the dissolution method, we have seen the model successfully justify a biorelevant method as well as the discriminating capability or lack thereof. Using it, we've been able to wind specifications but ultimately allow for the ability of the dissolution method to reject a non-BE batch, again, which is the goal of dissolution testing from a quality standpoint.

One of the other areas we've seen in silico modeling be successful is biorelevant specifications of CMAs and CPPs, which were discussed this morning, which are critical material attributes and process parameters. They were used to justify specifications such as particle size or polymorphic form, and process parameters such as milling method or pressure and force hardness and dwell time of the tablet punch, and of course in

SUPAC and risk assessment.

For example, a SUPAC level 3 change, which would require a bioequivalence study, we were able to waive using a previously established PBPK model. And again, the totality of data was used. In addition to that model, there was a balance of the other quality parameters, the clinical data, the dosage form, and the general risk to the patient.

What are some of the challenges we have seen so far? What happens when an application or dossier does not link that in vivo data to the quality data? If there's an understanding of the impact of the quality attribute on the in vivo performance being necessary for the benefit-risk assessment of the assessor, then an information request may be issued, and that is becoming more and more common.

We generally have cam [ph] [indiscernible] language that we send out because of this, and it's sent out at all stages of the IND, typically end of phase 2, phase 3. And it has been starting to go out for ANDAs as well.

Without it, we have to rely on quality parameters at hand and more of a traditional pharmaceutics approach, which is really just ensuring batch-to-batch consistency and sameness. This is often seen as regulatory inflexibility because we have to use traditional pharmaceutics so to speak and set specifications very tight without that insurance or link to the in vivo data.

One of the other things that we commonly see are two drug products or two comparisons may exhibit bioequivalence or relatively similar bioavailabilities, yet they show a difference in in vitro release characteristics.

The problem with that is a lot of times, QC methods are set under these circumstances, which may or may not be a big deal depending on who you talk to you. But the problem is that many of these same QC methods are used for batch release, and releasing the product as well as these FARs are out of spec, field alert and reports. The other issue is the same QC methods are now being used for biowaiver purposes and supporting post-approval

changes.

There is also functional and logistical challenges. Modeling is not an easy thing. They're very complex. In addition to that, not everyone at the agency is a modeler. So there's a training piece where our folks have to be trained properly for consistency sake. The cross program nature of our group, in OPQ, there's both PDUFA and GDUFA, and managing those, as they're dramatically different in the regulations and the approaches, and most importantly in my opinion, the timelines and deliverables. So that proves a logistical challenge as well.

From what we see, there's a reluctance to attempt modeling up front or to submit early development data, which may indicate that modeling is a possibility. The other issue is modeling with regards to PBPK is very application specific. Although we see in biopharmaceutics both innovator and generic drug data, not a lot of that information translates from one application to another; one, for legal reasons; but two, because

of the product being so specific and the model being so specific to that product.

There are software limitations. There's a wide array of software available depending on the company we see and the company's experience. We see different uses of different software. The ease of training and use varies depending on the software, and the data handling capabilities also vary.

Hopefully, I've painted a picture and gave you enough information to help move the conversation along. In conclusion, patient-focused quality standards are so far an evolving thought process and should be agile and flexible. From what we've seen, it provides for a high level of manufacturing flexibility as well as regulatory flexibility. And although challenging, in silico modeling is a promising tool in our space to support not just dissolution but patient-focused quality specifications.

Finally, NDAs and ANDAs conceptually and scientifically may be similar, but execution of the

model may actually end up being different due to the programmatic differences.

With that, Dr. Yu.

FDA Presentation - Lawrence Yu

DR. YU: Good afternoon, everyone. Thanks, Paul.

Rick gave us an update of the latest issue of the guidance for the immediate-release dosage form, highly soluble drugs, which we typically see in BCS class 1 and class 3 drugs. Rick also gave us an update in advances in dissolution apparatus, understanding in vivo physiology. And Paul gave us an update about advances in PBPK modeling and the two [indiscernible] here.

I'm going to talk with you regarding the bioperformance risk for extended-release dosage forms, and I'm hoping to make a case why we put so much attention and why we want to focus today on this extended-release dosage form because of the significant risk which the agency is facing today and the consumer is facing as well.

I use very similar slides from Paul, but

essentially it is biopharmaceutics links and product quality to in vivo performance. Many of us know that during the product development or drug development, typically we go through the phase 1, phase 2, and phase 3 clinical studies. Subsequent to approval, the manufacturer continues to manufacture the product put on the marketing place, and those products will now go through sophisticated, expensive clinical studies.

One of the two [indiscernible] we used is to ensure those products are still performing the same as the clinical material, and one significant test is in vitro dissolution. The significance of this test is part of the reason the agency puts so much attention on this very unique test. And in Paul's presentation, a significant point is that this in vitro dissolution test could be utilized in product development, could be utilized in product releasing, and could be utilized for biowaiver and the regulatory standard establishment.

So this is one simple test and has multiple utilities and multiple uses here. That gives

additional challenges opportunity provided to us.

With respect to risk, I use two specific cases, not exactly dissolution, but significantly involves a significant in vitro dissolution. First is vancomycin. Some of you were probably involved in the early 2000s, probably 2007 or 2004, the agency recommended in order to show vancomycin to be what we call bioequivalent, the sponsor has to use clinical method to show the equivalence.

Even though we do our method, it is clearly not practical based on the calculation from our statistician. In order to show vancomycin to be clinically equivalent, they have to recall every single patient in the United States, which is not practical. It's not useful anyway. So therefore, despite the fact the agency, FDA, does have a method, practically there are no generics.

In the middle of 2000s, 2005-2006, agency was working hard at developing the in vitro method, which is we in here call option 1, in vitro option. Then you come back to how much risk is faced. When we require similar formulation for product

dissolution, we have to feel confident that in vivo bioequivalence risk is very low.

Of course, the agency went through many challenges here, through the public advisory committee meetings. Eventually, the Office of Generics approved generic vancomycin for the benefit of the patients, and certainly the patients have used the generics happily and safely. So you can see when we develop a method, it significantly shows the risk we face.

I want to use another case, which does not absolutely relate to in vivo/in vitro relationship, but has an in vivo/in vitro relationship been established, certainly that risk could have been minimized. This is [indiscernible] a risk because this product was approved in 2006 and eventually withdrawn because non-equivalence in vivo.

This shows the risk we're facing that we call a bioperformance risk, which we discussed here today, but I will talk today specifically to focus on extended-release dosage form.

When we focus on the bioperformance risk,

this traces back what happened when patients take a solid oral dosage form or dosage product. When a tablet or capsule is administered, when a patient takes the capsule and tablet, those solid dosage form products well disintegrate and dissolve in vivo, in the stomach to start with.

Dissolved and undissolved drugs will be emptied from stomach and come to the small intestine, which the transfer graduates from the duodenum, jejunum, and ileum. Then the period of transformation, roughly 3 hours, the drug continues to dissolve, and absorption occurs. The drug crosses the intestinal membrane and goes through the liver, and eventually leads to the systemic circulation and produce therapeutic benefit.

When you look at it in vivo oral drug absorption, it sounds very complex because there's multiple factors involved here. But we do have one very well known scientist, Professor Gordon Brown from the University of Michigan [indiscernible]. In the early '90s, he published a paper and research in '95. He established biopharmaceutics

classification system. In other words, despite the complexity of in vivo oral drug absorption, he proposed to use two simple parameters to classify drugs. One is solubility and the second is permeability.

In the initial '90s, there were many follow-up discussions and of course a lot of controversy in the scientific literature. Now this biopharmaceutic system has been commonly used in drug development. Also, I cannot remember how many guidances at FDA utilized this system for dissolution, bioavailability, bioequivalence, and even multiple establishment of the quality guidance. I know our polymorphic guidance even uses this system as a guidance. So impact is hugely significant.

When we use this BCS classification system applied to establish regulatory standards for dissolution, first we need to understand bioperformance risk. If you look at BCS class 1 and class 3 drugs, basically BCS class 1 and class drugs are highly soluble. A very simple term, when

patient takes those medicine or this product, it disintegrate and dissolve rapidly in vivo.

For those products, the in vivo bioequivalence or bioperformance risk is relatively low unless there's a significant impact by excipients and so on and so forth. Therefore, last year, we extended biowaiver guidance. To give you a historic background, the classification system was established in '95. The agency issued biowaiver guidance in 2000 for highly soluble, highly permeable drugs.

Last year, we revised the guidance and extended this biowaiver from highly soluble, highly permeable, highly soluble and poorly permeable as well, which could be BCS class 1 and class 3 drugs. This year, just last month, we finalized guidance, which is discussed by Dr. Rick Lostritto, that specifically for BCS class 1 class drugs, as long as dissolution has dissolved 30 minutes more than 80 percent, we automatically accept this.

So even though we did not show you the in vivo/ in vitro correlation or relationships, in a

way it implicitly suggests there's relationship. But what that means is as long as you dissolve more than 80 percent in 30 minutes, the bioperformance risk in vivo is relatively low. In other words, there will bioequivalence. In other words, they will show similar safety and efficacy for those medicines.

In a nutshell, in general -- and I'll make a blank statement here -- bioperformance risk for BCS class 1 and class 3 drugs, the immediate-release oral drug product is relatively low or very low. Of course, you have to [indiscernible]. For example, you have to say these non-NTA drugs, [indiscernible], will disintegrate. You also make sure there's common sense that excipient does not impact. If you give a lot of [indiscernible] in the excipients, which is speeded up in transient time, certainly the impact will be significant.

In general, we can make a statement, for BCS class 1 and class 3 drugs, as long as it's not NTA drugs, as long as it's the older condition, which in Rick's presentation met the risk for

bioequivalence, in other words, the risk for bioperformance is relatively low. So the agency feels that for BCS class 1 and class 3 drugs, we have a good handle and good control about bioperformance risk.

Now we come to BCS class 2 and class 4 drugs, which are poorly soluble. When we talk of poorly soluble for all the other clinicians, what that means is for those drugs, the disintegration and dissolution in vivo may be slow. It may take a very long time. And there's a possibility it will not dissolve in vivo during the time of going through the GI intestinal tract, which roughly is in the small intestine for 3 hours and colon roughly 30 hours.

For those things, in theory, you could establish an in vivo/in vitro relationship, but because of the [indiscernible] issue, you say, well you have dissolution control, and therefore, you could have an in vivo/in vitro relationship. But in reality, it's not easy to establish because very few companies and sponsors actually attempt to do

them and some companies didn't do it. But the percentage established relationship for BCS class 2 and class 4 drugs are relatively low.

But the point I want to make is we recognize for BCS class 2 and class 4 drugs, the established in vitro/in vivo relationship, the chance is very low. However, typical formulation -- I just want to take the special cases we're probably not going to cover. In typical immediate-release dosage form, we have a good understanding when you take a tablet, how the disintegration becomes granule [indiscernible], and when it's granule, the drug particles eventually dissolve.

So the mechanism of a drug disintegration and drug release, dissolution in vivo is reasonably well understood. There's a reasonably good understanding in vivo, therefore, we have reasonable good control, not only just dissolution but drug substance, particle size control, and drug substance polymorphic control, and many other controls we potentially put in place.

One example in short, the bottom line is

that, frankly, this is one of the typical NTI drug, digoxin. When we use computer modeling, we pretty much can predict in vivo absorption based on particle size. In other words, what I want to say is for BCS class 2 and class 4 drugs, despite the fact that maybe the in vivo/ in vitro relationship is difficult to establish, because the CMC quality control is in place, plus dissolution in place -- we at least showed disintegration, and we have control -- bioperformance risk for BCS class 2 and class 4 drugs, those immediately solid oral drug products are relatively low or media.

Of course, I put a medium hint because if you do not understand what is going on, if you do not have good control of polymorphic form, if you do not have good control of [indiscernible], amorphous material or stuff like that, this could reasonably become high. But in general, and if you're confident that for BCS class 2 drugs, those are the immediate-release dosage form in vitro dissolution plus same controls, we feel confident in the quality of those products. We feel

confident that the marketing place leaves them in good shape.

That's part of the reason today's discussion, when need your advice and we need your input focused on extended-release dosage form.

Now, Paul mentioned about this specific guidance issue 20 years ago in September 1997. So of course, the agency, we want to keep them updated and revise the guidance to fit our current needs. This guidance basically establishes level A, B, and C. Different level would require different expectations.

Level A basically points to relationship between in vitro, dissolution, in vivo, and the level B is basically a statistical moment analysis. Level C is some kind of single-point analysis. For example, maximal, the percentage of drug dissolved in a given time, two of the main PK parameters, as such as AUC, Cmax, or Tmax.

Paul mentioned in his talk the issue on the PDUFA side, with new drug side, roughly 58 applications were involved here. Some of them get

FDA approval. But in general, the benefit of in vivo and relationship has not been fully utilized because of multiple challenges, which scientists are facing today.

As always, the in vitro dissolution is a very significant and important even for product development. I'll just give you one slide to show by design arena. We wanted to have an in vitro dissolution test to understand the impact of clinical material attributes or critical process parameters, and the CMC development.

During the product development, if we do not have reliable in vitro dissolution, in other words, we do not have a test for what they're testing for, it's incredibly difficult for us to establish what are the critical material attributes, what are the critical process parameters to control the process.

So therefore, without significant, predictive dissolution established, it's a challenge to ensure the quality in the marketplace.

In my mind, by performance risk for extended release, solid oral drug product without IVIVR is

medium or even high. Of course, I want to specifically say because it depends on the mechanism of the drug release. And somebody probably says, for example, metric system is simple dosage form, we could have good control.

I agree, but if it's a complex extended-release dosage form, the bioperformance risk in vivo is a high. That's part of the reason, as we discuss here, we need you on how do we move forward. I cannot emphasize enough because those regs are established and we do have some challenge we've faced in the past, we recognize the challenge.

We now say, well, we will require you to do IVIVR without recognizing the challenge and without recognizing the difficulty we're facing. The challenge we're facing here is the factors that affect in vitro dissolution is not well understood, well controlled. And in Dr. Lostritto's talk, you can see there's mod apparatus [indiscernible], whether it's two-phase, single-phase, or complexity. And none of them probably really mimic

in vivo exactly.

Number two, the fact is that in vivo dissolution is not a well understood. We recognize there's lately some publication out there, but really, there are few studies to show how the drug is released in vivo. We have tons of data on in vitro release, but we have very few data about in vivo drug release.

In order for us to move forward, we do need to establish in vivo drug release so we have a better understanding and when we know the target. When we understand the target, we can design better in vitro tools. If we do not target, certainly we're blind. When you're blind, certainly it depends on how lucky you are with the sunshine or raining. So it depends on which day you're doing.

Another area recognized establishes the absolute correlation for level A and level C in FDA's 1997 guidance. It's an incredible difficulty, but that's part of the reason we ask you for input on in vitro/in vivo relationships because we're advanced in PKPD modeling, which Paul

discussed. We feel there's opportunity. There's opportunity for sponsors. There's opportunity for us to take. Eventually of course, our beneficiary is our patient.

So where do we want to go? As we discussed quite a lot, I'm trying to make a case that bioperformance risk for BCS class 1 and class 3 drugs immediate-release dosage form is very low. Bioperformance for BCS class 2 and class 4 drugs, immediate-release dosage form is low and medium [indiscernible]. But bioperformance risk for extended -release dosage form without in vitro/in vivo relationship is low or even high.

Where is our future design state of in vitro dissolution for extended-release oral dosage form or oral product? I want to leave the thought here. We want to have an in vitro dissolution test that provides predictive insight to in vivo performance. This will assure high-quality drug products that maintain the safety and efficacy throughout the product life cycle.

With an in vitro/in vivo relationship, the

impact of critical material attributes and the critical process parameters or in vivo performance can be quantitatively assessed by in vitro dissolution. This provides scientific and risk-based knowledge to support patient-focused quality standards.

In a simple term, established in vitro/in vivo relationship for extended release oral dosage forms will significantly reduce the risk of the bioperformance of those products to patients. Thank you.

Clarifying Questions

DR. AMIDON: This is the point at which we can ask clarifying questions of our FDA speakers. If you have any clarifying questions for the FDA, please remember to state your name for the record before you speak, and if you can, please direct your questions to a specific presenter, and just let us know if you have questions, and we'll keep track of that.

Dr. Cook, first.

DR. COOK: I have two truly clarifying

questions, and I'll go with Lawrence first. Just so when we get to the question, are you looking for this patient-focused dissolution standard to rely on release testing and overall quality of the formulation in IVIVR set [ph] release, or are you looking only for the former?

I'm wondering if you're looking for a method that would be robust enough to use for release testing, and then I'll have my comments on that later because that's the comments part.

DR. YU: At this moment, certainly we could have two dissolution methods. One is in vivo quality to show it's safe and effective equivalence, and that dissolution method is now more commonly used as a QC test.

DR. COOK: The second one is for Paul, and that has to do with the use of a PBPK or PBBP. You mentioned that 75 percent of the ones submitted that used PBPK were successful, and earlier 40 percent overall since 2008 weren't successful. That leaves two that weren't accounted for.

I'm just wondering, in a case where somebody

submitted they used PBPK in the development of the IVIVC but didn't develop the IVIVC using PBPK because they needed individual predictions, was that counted as a PBPK use or not use?

DR. SEO: That's a great question. There is some overlap, not as much as we'd like to see. But I would count that as a use, primarily because in the instances where -- it's not a lot yet, but in a couple of instances where we've had a PBPK case support an IVIVC, we were able to salvage some of that information.

DR. AMIDON: Good for now?

DR. COOK: Yes.

DR. AMIDON: Next, Dr. Awni, please.

DR. AWNI: I was wondering if you have -- like to declare something as valid, a PBPK in a biopharmaceutic sense. Have you start defining the parameter of validation or what is acceptable or not? I think that's far off. I just do a comment on that. Part of the thing is the comfort level is if we do develop something, would that be accepted? So do you have success criteria?

DR. SEO: It's hard to put a specific number. We've been asked that question a lot, and it's hard to say here's a line in the sand. If you're on this side, okay; if you're on this side, no, because that's kind of the situation we got into with IVIVC.

So far from what we've seen with regards to PBPK or quality in silico modeling, each use case is slightly different. Each user's experience and knowledge of data for that product is slightly different. So the level of risk that we're willing to take changes, and therefore that variability in the model or validity in the model also changes.

DR. AMIDON: Good. Thank you.

Dr. Tenjarla?

DR. TENJARLA: Thank you. Srini Tenjarla, Shire Pharmaceuticals. My question is specifically for Dr. Lawrence Yu. I completely agree with you that there's a big challenge for extended-release dosage form to match the in vitro dissolution with the in vivo profile, mainly because we are limited by what we could do by the traditional dissolution

methods.

Has there been any thoughts given to other models out there like the TNO model, the simulated gastric model for dissolution testing and the physiological development conditions?

DR. YU: So what we're looking for is a kind of in vitro dissolution test, and not necessarily USP dissolution test. So we're opened to other possible input regarding the dissolution apparatus test method, media, and include approaches. For example, we're not strictly looking for in vivo/ in vitro correlation, which is defined in 1997 guidance. You could have used potentially a PBPK modeling instead of potential relationship.

So at this moment, the challenge is there and the desire to go is also there. But how to get there is wide open. We are seeking the advisory committee's input on this. Thank you.

DR. AWNI: I think that makes sense because in the past, we have evaluated simulated gastric fluids and simulated intestinal fluid. At the same time, we also use the models like the TNO simulated

gut model and some of the other stuff we did. And basically combined together, you get a lot of information. But that's actually very good for doing it once or twice, but it's very difficult to do on a routine basis for a batch-to-batch release.

DR. YU: We understand, yes. Besides the USP apparatus, there are multiple apparatuses out there, and Dr. Lostritto in his talk introduced a number of methods and certainly [indiscernible]. The company or sponsor can choose whichever method they want. But the bottom line is when you collect all this data, all this information, when you have an enriched knowledge, we begin to understand and we can make progress.

If a company, the one or two that was never shared with us, it's very difficult for the agency to make progress. We all continue to rely on dissolution apparatus in specified USP method. We recognize the very complex TNO method if you want to use for daily -- as a quality control and could be very complex, but we have to start somewhere. We recognize that. Thank you.

DR. AWNI: Thank you.

DR. AMIDON: Dr. Sun, next.

DR. SUN: I have a few comments for challenging and opportunity. I also have a question. I think it's really exciting to see FDA went a long way to really accomplish a lot of a good things for immediate-release dosage form, all the new technology to really test the quality to ensure the safety and efficacy for that. That part is really exciting to see.

I totally agree with Dr. Yu's presentation, the last for IVIVR for ER. I think that's long overdue. The challenge I see is that. To ensure the safety and efficacy from a quality point of view, even from an innovator ER, that's first a challenge already there. So from IR to ER innovator, that's a lot of unanswered questions still there. And from innovator ER to generic ER, that's another level of uncertainty. So that's one challenge I see.

The second was in terms of modified release, some drugs have a really modified release, you have

a traditional flip-flop, and some other drug will not. The question is which one is really true a modified release? That's another challenging question that needs to be answered.

Third is, for SR, which is twice a day, versus ER, which is once a day, there's also an unanswered question there in terms of bioavailability.

The fourth is regarding the IVIVC, the in vitro by irrelevant conditioning, like the voting [indiscernible], the buffer capacity, the time, the stomach, some intestinal [indiscernible]. And especially for calling for modified release, that's just very much unknown. So really I see -- I think there's a lot of opportunity and a challenge there. And now in the last few years, I agree with Dr. Seo, as to why people don't like to do IVIVC, because it is challenging. We made a lot of assumptions, which we don't know.

For IR, IVIVC and PBPK works reasonably well, although we made an assumption in vivo. But the ER for those assumptions no longer work. So I

think that's where the challenge is. Of course, we can manipulate -- not manipulate, modify the model to fade the IVIVC. But the question is how do we know that's correct? How do we validate? So that's the condition. How do we validate in vitro biorelevant dissolution, all those conditions? How do we validate in PBPK to make sure we can capture all those answers?

So those are my comments for the challenge. And the question is, those situations are different from this morning's discussion. This morning, you have all the knowledge in the basement. You can gather that. The problem for here is there's no knowledge yet. Nobody has this in vivo data. We don't have it to validate, so I don't know.

From the agency's point of view, what are your thoughts? How do we gather those data to really move this forward? This is long overdue for modified release.

DR. YU: I want to clarify. I know in our Federal Register notice, when we initially want to discuss this topic for the discussion at this

meeting, we used the words "modified-release dosage forms," and we made a change to extended-release dosage forms, partly because we need your input to be focused because modified-release could be extended-release dosage, and extended-release dosage form could be delayed release.

So I'm hoping this afternoon the discussion will be focused on extended-release dosage form only so that we can get input, and agency can continue to make an effort. Although the goal is I'm hoping we make some progress in this specific dosage-form arena.

In terms of agency planning, the answer is simple. We need to get more data. How to get more data, you need to fund it. The agency, whether private sector, industry, academia, we all need to be -- this whole scientific community, bringing it all together and identify areas we need to be working on, get additional data, what we need so that we can make it progress.

The chair, Greg Amidon, besides this voting question, if the committee could provide additional

recommendations and suggestions to the agency, I will personally be very appreciative. Thank you.

DR. AMIDON: I have a question. This is Greg Amidon. This is directed I think to Dr. Seo, please. I think you touched on this one, at least in part, when you were answering Dr. Awni's question. But recognizing that users when they use software for modeling purposes maybe have different levels of experience, and you take that into consideration, I guess my question's a little bit more about the software limitations and the wide variety available.

That software is proprietary. Some of that is black boxed perhaps. And I'm just wondering what your thoughts are in terms of how the FDA would address those differences and issues and unknowns, and the potential that with two different packages of software you could get two different predictions, I guess I'll say.

DR. SEO: Also another great question. The agency recently released a guidance on the format of PBPK and the acceptance of those kinds of

models. Part of that has to do with assumptions, getting us information with regards to any kind of black box information. Even the innovator or the company might not have that information, but if there is such a situation, particularly whether it's software based or perhaps they're using their own code to create the model, we ask for.

We by no means can have an idea of what those black box assumptions are. We put it on the sponsor to explain to us. We're not here to do a review and really re-do the work. We're here to make a critical assessment of what's been done.

The other piece is we regularly have interactions with the companies of the software, the manufacturers that code it. And they ask us on a regular basis, either in hallway conversations or at a workshop, what do you need and what are you lacking? They look for process improvements, and we give them that feedback. So some of that has been incorporated, and we hope to see more of that collaboration moving forward.

DR. AMIDON: Thank you. Dr. Polli?

DR. POLLI: Jim Polli, University of Maryland. I have a question for Dr. Lostritto. Thank you very much for your talk on patient-focused quality standards. I enjoyed it very much. If I understand, IVIVC has been around for over 20 years at least in guidance form and has been recommended for some time. And to some level of extent, it's been applied, but maybe not nearly as much as probably all of us would hope, really. So the question that comes to my mind is how to motivate busy developers to also engage in this area a little bit more.

What I noticed, Dr. Lostritto, in one of your early slides, you talk about there's opportunity to avoid under- and over-discriminating. Do you see opportunities to move the field forward in terms of benefiting developers and patients in terms of using this type of dissolution approach?

DR. LOSTRITTO: Yes. Thanks, Jim, very much. As Dr. Yu mentioned, too, we're open to other types of in vitro approaches besides the USP

apparatus, number one. Secondly, we do get a lot of interaction with the industry on what's over- or under-discriminating in terms of dissolution, and it generates a lot of discussion. I think the reduction of things, methods that are over-discriminating when not necessary would be I think of high interest and would serve as a motivation to develop that relationship or correlation.

You look at dissolution as a tool. You want to refine it, and sharpen it, and hone it, and that's a great idea. But sooner or later, it starts coming down to the minutest thing you can measure theoretically. Just like we run into the same problem with impurities and assay and so forth, you can get lower, lower, lower and tighter, tighter, tighter, but is it relevant physiologically?

I think not only is there a scientific value in that, but there's a very practical value in being able to have a method that is reflective of the proper level of discrimination that is

biorelevant, number one. And also, as Dr. Yu mentioned and maybe Dr. Seo also mentioned, too, one size does not fit all. You may need a method that serves this purpose to do occasionally and have that correlated with an in vitro method.

So instead of correlating every in vitro method to an in vivo situation, once you have an in vitro/in vivo relationship, then you only need to connect your in vitro to that second relationship, kind of a secondary standard so to speak. And I think that approach has some value, too.

Does that address your question?

DR. POLLI: Yes.

DR. LOSTRITTO: Thanks.

DR. AMIDON: Dr. Terzic?

DR. TERZIC: I also enjoyed the presentation. This is Andre Terzic from the Mayo Clinic. Dr. Seo very clearly pointed out the significance of this discussion, and he framed it in one of his slides as part of the ethical, even, consideration of if we could, in an ideal world, even avoid in vivo studies and rely increasingly on

in vitro studies, one of the ethical aspects will be there even more focused. And the biowaiver program was highlighted very clearly.

Just as a suggestion to our colleagues at the FDA, actually the terminology that you use in the title, the two terms that caught my attention that may need some internal clarification, the first one is actually "patient focused." When you say patient focused, there is an automatic reaction that beyond biorelevance, which you define more as a physiological concept, there is a pathological dimension.

Are diseases in one or another maybe not affect the dissolution per se, but affect the other piece, dissolution information that Dr. Yu put together in the formula. For you to think a little bit, is patient centric really or patient focused really what this effort is attempting to do, or does it require a pathobiology beyond the biology or the physiology to be addressed?

That's one. The next one are the standards. What specific standards are you really after? This

will be very useful to delineate from the onset. Then we may be able to more specifically help you with the categorization of these standards as you keep on building them. But that's maybe an ongoing discussion and doesn't need an immediate answer. Thank you.

DR. AMIDON: Dr. Slattum?

DR. SLATTUM: This is Patty Slattum from Virginia Commonwealth University, and I have actually the same question or concern about what the term "patient focused" was intended to mean. Because I agree about the pathophysiology, but I also think of what the dimension of normal physiology even can span.

Is the ultimate goal to help us to understand those sources of variability better or to understand the dosage forms performance better?

DR. YU: So maybe I'll give it a shot to see if I can answer your question. Some of you know me well. I come from industry. When I was in industry, I always asked, "Why does FDA want this?" The answer is because FDA wants it. When I joined

FDA, I questioned, why are we doing the test? "Because we want to do this test."

Sometimes we do the test. What is the purpose? It is not very well defined. The dissolution is a typical example because dissolution is the only way we understand the drug release, so therefore the test must be conducted. But the problem is in some cases it not may be related in vivo. If it's not related in vivo, then for what purpose?

So therefore, we are here to discuss -- the agency feels that we need to move all the quality standards, industry sponsors, move and be related to the patient. If it's not related to the patient, then testing may not be meaningful and may not be needed to do those tests. That's the whole bit behind disease.

Certainly, I recognize from clinical, from the physician's perspective, when you call a patient, are we going to talk about pathology or other related? But mainly, folks, I want to emphasize. That's why in my talk, I specifically

emphasize the bioequivalence and predictive power to ensure the product manufacturers continue to perform same as material in the clinical studies. That's the whole purpose we're talking about here. Thank you. But we have no meaning -- the extent to different disease material -- different disease state, which is very complex. But at this moment, we want to talk about standards, which is relevant to clinical studies.

DR. SEO: And just to clarify, I think "patient" is the right terminology because what we're really starting with is safety and efficacy profiles. With regards to if there's a minimum concentration to elicit the effect, whether it's a kill rate in an anti-infective antibiotic, or maybe there is an adverse event that you're trying to avoid and you want to limit the Cmax, or in the case of extended release, you need to elongate that profile so they have an all-day release, it really does start with the patient and the intended indication for that drug product.

PK is a surrogate of that, which primarily

we use to set the dose, and in our case help set the standards or the specifications from a quality perspective. So just to add on to that, I think that patient focused is probably, in my opinion, relatively accurate. Maybe others disagree. I don't know, but just to clarify. Thank you.

DR. SLATTUM: Can I just follow up for one second? You mentioned in the PBPK the case would be for actually incorporating those sorts of things. You mentioned special populations, whether the absorption would be the same, and maybe that is where this link to patients is happening.

DR. SEO: Special populations is not in the realm of responsibility for OPQ. Our colleagues in OTS and clinical pharmacology deal with that, but again, in certain cases, they [indiscernible] falling for that purpose. The intention of that slide where I went over that was to show the various uses in CDER, not specific to OPQ. Thank you.

DR. AMIDON: Dr. Mager?

DR. MAGER: Thank you. Don Mager University

of Buffalo. I also was thrown by the patient focused when I first read it. I get it, and I get into the FDA's point on it, but it didn't immediately imply to me that there would be some level of disease that you were trying to incorporate into the standard. So I think it just needs to be very clear, I guess, and it wasn't by the title. But of course getting through, I understand it.

I would really like to see mechanism-based modeling put into it. It's probably no big surprise that a modeler likes to see more modeling at the FDA. So it's not a big surprise there. But I did want to go towards the objective. And that is, with all of the focus on PBPK and doing modeling in a better and more sophisticated way, are you looking for model agnostic standards, or are you envisioning standards that are coupled with the pathways that you're going to allow?

So if you're going to do a PBPK, you'll get these standards. If you're not going to do PBPK, it's a different set of standards. So are you

looking for something that's model agnostic or do you wish to actually couple this with modeling?

DR. SEO: It would be the more of the latter. So it would depend on the selection of what you're trying to do. In a nutshell, model agnostic. I don't know if that answers your question.

DR. MAGER: Oh, no.

(Laughter.)

DR. YU: Can you elaborate a little bit more about details?

DR. MAGER: Yes, of course. You made the point, and very nicely, that the model criteria are application specific. If you're modeling criteria that are going to be application specific, how will you then set aside standards that are separate from the methods you're going to use to establish the relationship between in vitro dissolution and in vivo performance?

I can envision ways you would do it in terms of PBPK. Similar to the way it's done for pediatrics, you would have a model that's perhaps

validated in adult subjects before it's ever applied to a pediatric subject. So you can envision PBPK being applied to immediate release before it's applied to the extended release, so for the same compound.

So I can see ways in which -- and you have great guidances out already, so I'm fine with that. But when you come to then dissolution standards, how easily then can you separate and create general standards that are separate from the method you'll use to actually establish those relationships?

DR. YU: I'll give a try to see if I can answer this question, to see if I can understand this. The typical PBPK modeling and the absorption predicted in vivo is I would say different from typical pharmacometrician, which is involved here. Those models -- I'm sorry; I have to mention my own model, just comparing absorption transit [ph] model -- is based on a physiological term as reasonable established.

So when you plug the drug substance or drug product information into this model, where models

already exist, we may shift one or two parameters, but it's not random. It's a brand new model. The CATA [indiscernible] model original was established based on the standard physiology in vivo.

Now with the sophisticated understanding of an in vivo gastrointestinal tract, we may continue to improve this model. But this model is now continued to revive and have a better fitting about in vitro dissolution and in vivo. So there's a lot getting involved, so I'm not sure I answered this question, but I feel probably it's different here.

DR. MAGER: No. I wasn't trying to distinguish fitting from projections. The use of PBPK, I got that. But how do you set a standard, then, without PBPK? Do you see what I mean? Are you going to require PBPK? I should say is PBPK going to be required for every application?

DR. YU: At this moment, we're seeking for some kind of relationship to be established with PBPK as a tool, facilitate establishment for those relationships. In the 1997 original guidance, there's no mention of a PBPK. So in a very simple

term, you have an in vitro dissolution, a profile percentage of drug dissolved as a function of time, and you have pharmacokinetics, and [indiscernible] the pharmacokinetics.

So you get a percentage of a drug dissolved in vivo, and we could have a point upon the relationship, for example, 10 or 20 minutes, he has 20 percent dissolved in vitro, and in vivo 30 percent is up, so we kind of have a linear relationship. But now, does this term -- there's no sophisticated PBPK. It's a simple, linear relationship but involved.

So we're open to suggestions. We're not specifically saying you have to use a PBPK model in that relationship. We're open to all kinds of relationships. As long as there's some kind of relationship, which is validated, we should have a predictive power. I hope this answered your question.

DR. MAGER: Thank you.

DR. AMIDON: Dr. Cook, did you have a comment or question specifically on this?

DR. COOK: Yes. I thought I'd try to rush to the aid of the FDA. Jack Cook, Pfizer. The idea is that the standards assure a level of safety and efficacy, so that should be agnostic to the model you're using, whether you use one or the other. So that's why the goal is to assure that to the same degree.

So if you're predicting Cmax and AUC as the surrogates for safety and efficacy, the standard, regardless of the methodology, you should use if you want to ensure the same amount of safety and efficacy confidence, should be the same regardless of model. And I think that's why you were saying model agnostic.

DR. AMIDON: Dr. Awni?

DR. AWNI: I was going to go back actually a couple of statements that, Dr. Yu, you mentioned, which is basically to say, depending on -- I've been in multiple discussions where there is discussion about, well, we need a dissolution method for quality and lot release, and we need a dissolution method to do IVIVC.

Those two things, this could be simple. This could be much more complex. And I think the more you guys, you guys meaning the FDA, come out with a little bit more description -- because you said I think, if I understood, it might be two different things. The more meat you put on that statement, the more you separate the two, then probably the more interest in actually saying, hey, if I come up with a very sophisticated in vitro dissolution method that I related to in vivo, am I going to be using that for lot release or quality?

So the more guidance you give about when do you do that, how do you do that, that will actually help move it because then you really focus the IVIVC and patient to things that are -- we did formulation changes, we did all of these things. Now we're going to use this method to do this to accomplish, but this is a different objective, and you might want to have a different dissolution method.

DR. YU: I cannot agree with you more. So today's discussion, we're focused on some kind of

in vitro testing, simple or complex, which is later in vivo. In the hypothetical situation, if you do have a method which is later predicted in vivo, that will facilitate product development. That will facilitate the understanding of the critical formulation factors, the material attributes, and understanding of the manufacturing process.

In this scenario, we made not need to do drug release testing at all if we have a good understanding. In fact, the agency already approved a couple of the real-time released testing without in vitro dissolution testing. But at this moment right now, if the in vitro test is not predictive, what do we do? We're trying to put all the nails in place to control everything, and anything changing becomes a high risk because we really do not know what is going on. It's like a black box.

But in the future, which we're pushing for, if we have a good understanding -- if you've done a method able to predicting in vivo supposedly exist, then you'll have an understanding what are the

factors to get your results. If we have a good understanding of factors, you control this factor. Then the quality control method may not be needed at all.

But at this moment right now, we are not at this stage, so you probably can see from us, we want this, we want this because we have a poor understanding of what's going on in our way for extended-release drugs. To a certain extent, I don't want us to complete a black box, but at least a gray box right now. In the future, if we understand everything going on and we have transparency going on, then I do envision someday some in vitro so-called quality control dissolution test may not be needed.

So that's why I make a joke at the beginning. Why do we need a dissolution test? Because FDA wants it. Why does FDA want a dissolution test? Because in vivo bioequivalence prediction, if it is predicted. If it's not predicted, what is the purpose? For quality control. So what is quality control purpose? If

you go back to Dr. Kopcha's initial discussion, the quality is to make sure the next dose is equivalent. But with quality control, you have a test, but it may not be a test for the next dose is exactly the same or not.

So we make all the circular argument going on here. That's part of the reason. We are hoping we have some kind of test. Simple or sophisticated, truly predicting in vivo will make industry, sponsor, and FDA's life a lot simpler, but eventually the benefit is our patient.

I don't know, Mike, if you wanted to make comments here.

DR. KOPCHA: This is Mike Kopcha. Just a couple of things. One, we talk about risk base, so we need to know where the risks are. Obviously, if we don't know where the risks are, then we're going to test everything, and that takes a lot of time, a lot of money, and a lot of resource. So we're trying to move away from that.

So the more we can do these IVIVR situations, the easier it makes for us then to

figure out where to test, what to test, and what that actually means. It's tied back to the patient, because we've got individuals that come back and say, "You know what, Mike? We're doing all this testing, we've got our specification and stuff for the product."

But is that really clinically relevant, that specification? What does that specification actually mean? "Well, Mike, we're just able to control it, and that's what we're showing you." It's like, "Yeah, I know that, but how does that relate back to the patient?"

So as we talk about patient focused, what we're talking about -- and again, I know we already discussed this, and I think the clarity is there. We want to make sure we're focusing on what's relevant to the patient or what's clinically relevant, because if we set specifications that have no clinical outcome or no clinical quality, what's the point of that then?

So we really want to try to move away from just setting specifications for the sake of setting

specifications and really getting it back to what's important to the patient and getting them the drug, and the amount that they should, and so on, and so forth. So it always goes back to safety and efficacy, which is one of the reasons why I define quality as safety and efficacy of the next dose. So hopefully that kind of ties some of that together.

DR. LOSTRITTO: I just wanted to add to the discussion the thought that we should also keep in mind those things that destroy predictability as well, as we learn more about the in vitro and in vitro/in vivo relationships. For example, we know that over many years of study and research and publications, surfactants don't do much to bridge our relevance. We also know that USP apparatus, certain agitation speeds, for example, with the paddle, 100 rpms starts getting -- you lose discriminatory capability.

So as important it is to bridge and establish new correlations, it's important to keep in mind and to avoid those things we know detract

from that correlation as well.

DR. AMIDON: Thank you. Dr. Tenjarla?

DR. TENJARLA: Thank you. Srini Tenjarla, Shire Pharmaceuticals. I just have a comment on the request of can we focus specifically on the extended-release dosage forms and the fact that the number of applications that you got for IVIVR since the last 20 years has been a very small.

I think one of the factors that that needs to be taken into consideration is certainly limitations that we may not be able to do much about because we know that for extended-release dosage form, depending on how it is formulated, a significant amount of the drug is going to be released in the large intestine.

We also know that not much drug is going to be absorbed from there. And even if you did absorb, it's going to be highly variable because of the presence of fecal matter, because it may be that one tablet is going to be pushed harder by the housekeeping [indiscernible], or GI motility, that kind of stuff, so the variability is pretty high.

And for all practical purposes that's something we will not be able to control today or anytime soon.

But my point specific to the small number of applications that you have received for IVIVR is maybe because that everybody does a phase 1 study early on during development. And then if you use the phase 1 PK data and then you try to do a simulation as to what it will take for you to pass an IVIVR criteria for AUC and Cmax, it'll come up into a pretty big sample size.

For example, if I recall right, about 60 percent or 55 percent of a drug is being released beyond the small intestine, and if you do the sample size for you to pass the IVIVR, you're looking at pretty close to like about 200 subjects, or 125, or something like that, which may be one of the reasons why people are not really jumping to do an IVIVC for an extended-release dosage form.

My final comment is that if there is -- and I'm not an expert on it, but if there are certain simulations that can be done, especially for a drug

that is not really potent, where we are able to eliminate a certain part towards the end of the release profile, the large intestine profile, and at the same time scientifically being very sound when you compare the first 65 or 75 percent of the peak AUC, that may be probably something that's probably more agreeable to the applicants.

DR. YU: Thank you. So therefore, we're seeking the advice and input of pharma [indiscernible], and we recognize some of the challenges in the 1997 guidance. We don't want to introduce the PKPD model in this arena because in many generic innovators, when they develop the extended-release dosage form, you probably conduct more than one bioequivalent studies. When you conduct more than one bioequivalent study, [indiscernible] bioequivalent study, if you use PBPK model, you can learn significant knowledge from that. And I'm hoping they begin to move this direction. A company can learn from results and failed bioequivalent studies. It helps establish eventually the dissolution method, because it's

better than nothing. Right now, we're not doing -- all this knowledge, we're not getting.

So I'm hoping to open the door for all the opportunity and also, clearly, if FDA needs to show flexibility as well. As a scientific community, with the regulators or industry, we kind of need to work together to advance this whole field. Otherwise, 20 years from today, we will talk about the same thing here. Thank you.

DR. AMIDON: Just as a heads up, we have Dr. Polli, Donovan, Cook, Li, and Sun. We have some flexibility on time, so if there are others, I think we can get through these questions and comments. And if there are others that have questions, let us know. So let's go to Dr. Polli first.

DR. POLLI: James Polli, University of Maryland. This question is for Dr. Seo. I'm pleased to hear about the relative success in the modeling area in terms of biopharmaceutics. When you spoke about IVIVC and IVRs' current state, where there's been less success, you have one

question in your slides, "Why not more IVIVCs?" And one of the possible reasons that you suggest is it's seen as an all or nothing approach.

So I'm just kind of wondering, can you elaborate more on that? Is there anything that any of us or all of us can do, especially given success in other areas of modeling, where it doesn't necessarily have to be all or nothing?

DR. SEO: So generally, what we meant by all or nothing has been when the model was shown from -- around the framework, the guidance is set up. It's very difficult to salvage that data into something usable, particularly because most of the times right now when we receive an IVIVC, it's not for the typical quality purposes, typically because they're pursuing a biowaiver post-approval. And to do that, if all the benchmarks aren't hit as laid out by the guidance, we really can't grant that waiver.

Really, it just is a line drawn in the sand for that purpose. What can you guys do, the second part of your question. I guess vote yes --

(Laughter.)

DR. SEO: -- if I had to say anything. But it's hard to say, to be more willing to work with us up front from an industry perspective and pursue from an academic perspective more of these kinds of research. I think right now, we're just starting to open up what's possible with regards to manufacturing and using this kind of modeling. So I'm very optimistic. Thank you.

DR. AMIDON: Thank you. Dr. Donovan?

DR. DONOVAN: Dr. Maureen Donovan from the University of Iowa. I'm both trying to understand and simplify, and I'm afraid that I've probably oversimplified in my head what the goal is. So my first question is sort of a reality check, and then I'll follow up with perhaps the picture in my head and the struggle with how one would do this.

So here's my oversimplification, that the long-term goal -- stuck in dissolution testing. Sorry, Dr. Yu, but I can't get past that, so I'm going to stick with dissolution testing as an endpoint test, that is both something that somebody

can use for -- that will be used for product quality testing.

Are you essentially asking how that test is conducted, whatever the choices are, has a physiologic relevance to why time points, pHs, flow rate systems, whatever is being used there, that you can tie a physiologic relevance to those testing time points and the readout when all is said and done?

I'm starting at the end rather than the beginning. The beginning all had to be done, all of the modeling and whatever to understand potentially what the physiologic controls were, but are really what you're looking for, at the end of the day from an applicant, from a product quality standpoint, is that their dissolution testing methodology has essentially a justification that we draw at these time points, we use these conditions, and they have these meanings physiologically? And if we fail in any of these, it means something about our product, and that batch failing?

Have I oversimplified what you're looking

for?

DR. YU: No, you did not -- what we're looking for long term is that there's a dissolution test, which is predictive in vivo, which is related to in vivo. This dissolution test may be a useful QC test, but we can talk about this because I don't want to be a sophisticated test always utilized for batch release.

But if the envision of this test is to truly predict in vivo, then QC test, which is normally traditionally conducted could be simplified by control of the process, control of the material, and we may not need to conduct end-product testing at all.

I want to make sure of that because otherwise, companies say, well, we have to develop a predictive dissolution test. Now we have to develop another simple QC test. And the real question, what is the purpose of the QC test? For the QC test -- what is the quality? As Dr. Mike Kopcha defined many times, the quality is to ensure the next dose is safe and effective and equivalent.

Then what is the purpose of QC? Is QC just for process control or is QC just for manufacturing control? So the meaning of the QC has become questionable, but today how are here, we are looking for the opportunity to have a test which is related to in vivo.

DR. DONOVAN: Then my follow-up is, my second entering complex extended-release dosage forms is if I have a dosage form that by design, it delivers the drug in two pulses plus an extended-release component. So I'm going to get some changes in my plasma concentration time profile in my patient over time. But those have no clinical readout, those differences when I'm at my Cmax 1 and my Cmin 1, and my Cmax 2 and my Cmin 2.

I see no clinical differences, yet my performance test may somehow be tied to Cmax 1 and Cmax 2, and I don't see, one, the relevance or the necessity of that. And that's another thing I'm struggling with is that if really what you're trying to do is be predictive -- I understand from a quality control standpoint that you want those

pulses to be the same from that dosage form, but it has no clinical relevance whether they are or not. So this is where we are. Could potentially some of these new requirements be now over-regulatory?

DR. YU: We can have -- I don't want to say extensive. Myself, I have many experiences of so-called combination, immediate release and extended release become like a peak 1 and peak 2.

Let's go back. Why do we need the combination in the first place? When the company submits an application, than usually the application, instead of two-piece of combination, must have a clinical meaning. Otherwise, how will the [indiscernible] be approved.

So therefore, whether peak 1 or peak 2, there's a clinical meaning behind this. When you have a clinical meaning and the next is [indiscernible] establishes a surrogate, which is a bioequivalence criteria, which is relayed to in vivo performance -- you talk model peak. So when you have a bioequivalence criteria, a typical bioequivalence criteria, the experience is typical

Cmax and AUC, but not necessarily. We have a pash [indiscernible] AUC involved. In the area of [indiscernible] AUC, we can have a Tmax involved.

So there's a sophisticated expectation involved. What we're looking for in vitro, is despite the sophisticated expectation involved in vivo, some kind of dissolution test relates to in vivo multiple performance. That's what we're looking for.

So when you say, well, I have a multiple peak, but they're not of clinical relevance, my first question is how could a product be approved if they're not of clinical relevance? So I think there are multiple implications involved here.

I'm sorry, Professor Maureen Donovan. It could be much more complicated when you talk about specifics. That's why I want to focus on extended-release dosage form only so that makes hopefully our discussion more targeted and much more simplified

Does that make any sense to you?

DR. DONOVAN: It does, but I think perhaps I

wasn't clear about what I thought was a relatively simple occurrence in an extended-release dosage form. But in trying to think quickly of how to -- I guess maybe another way of making my point about clinical relevance is that plasma concentration isn't necessarily the best readout of product performance or clinical effectiveness. I mean, this is more of a PD argument, and I'm --

It would be really difficult to do a PKPD type request, so that's excessive. I certainly appreciate, but I'm concerned that with the focus on the plasma concentrations, that, again, some of the requirements for the IVIVC or the PBPK modeling become over-predictive or over-assessing a particular need.

What I'm trying to say is I understand in an individual product, that that's necessary. But as I start to think about ANDAs and whether the exact match of a profile that has no clinical readout, it's just a challenge to -- I'm sure the FDA thinks about that and has no response. And I'm not asking for one, but it's what I'm struggling with. With

this stage of this, it's not very far down the path to ask that question and how to provide information to the FDA that I think is useful and won't have to be stopped and reevaluated not too far down the path.

DR. YU: So I maybe answer two ways. One is to come back to the comments, Dr. Mike Kopcha made, related to the risk based. What kind of risk are we facing? We know the in vivo target. But when the in vivo target is unclear, where the PK is not predictive, certainly these things are very sophisticated.

I have been with the agency for many, many years, and one of the products we involve, myself involved, I look at it extensively, look at the possible clinical indications, and the PK profile feels like there is some risk and I'm not quite sure. But a potential risk may not be high.

When you approve this and the patients come back with multiple complaints because of their equivalence issue involved here, part of the reason is the following. When innovator puts a market in

place, there's a patient population. But when the generic comes, that actually focuses on not all, every single patient. There's actually a small percent of a patient, which is the innovator, which is already effective.

So therefore, the generic comes. You have to be in a way absolutely equivalent to innovate that. If not, potentially two subjects are not equivalent [indiscernible]. Now, in statistical terms, it may not be relevant, but if used 1 million times, if 5, 10, or 20 patients are not effective, they will impact it.

I often find it a difficult argument for the overall 1 million population, you find, well, only 3 percent, and the difference will not be statistically significant, so therefore not relevant. But that 1 million patient, when you talk about half million, which is already uses product, which is already effective, if a generic come in, there's some significant -- some change among this population, now the difference becomes very significant. In the marketing place, people

begin to recognize the difference. Frankly, my own experience, I look at a PK and saw it's no big deal, but at the end, it's very significant. The agency is very cautious in order to improve the subsequent change of innovator or generic, one, to make sure they're indeed absolutely equivalent to generics.

DR. AMIDON: Thank you. Dr. Cook, did you have another point to make or comment?

DR. COOK: I didn't at the time when I said no, but now I want to go on a couple of things. First, I think what you're talking about, Lawrence, switchability [ph], and I don't think that's necessarily on the table today to talk about. I think, back to answer your question, why we often have really good relationships between what drives efficacy -- and maybe it is AUC and you don't need to worry about Cmax -- we don't often have the same handle on safety.

So I think that's why often we may have what some people might consider an extra parameter in Cmax to look at just because we haven't developed

that relationship to know what exactly drives it. You can always do a efficacy study to get your product done, but nobody does that because it's actually harder to show equivalence of two formulations than it is to prove that your formulation works versus a placebo.

So we default to the PK, and when we due PK, everybody has decided that a 20 percent difference in Cmax probably is going to be okay. That's probably even more on a safety side for most products than it is on an efficacy side. So that may be one of the reasons why it looks like an extra standard when it's not needed.

I don't know if that helped you on your question or not.

DR. DONOVAN: That's a bit of a tangent, but it's okay.

DR. COOK: Okay.

DR. AMIDON: Dr. Li?

DR. LI: Tonglei Li from Purdue University. I definitely shared FDA's vision of IVIVC or IVIVR. I think it's important not only to ensure the

safety and efficacy of drug products -- and also, again from a drug development perspective, I think if can also help rationale design of formulation and product quality.

I just have a general comment or suggestion to express a point raised by Dr. Yu in your last slide. For me, I think any future development of the dissolution test need to consider drug absorption or permeation, whether that's done implicitly or explicitly. From a chemical kinetic or a mathematical perspective, I think the current approach is an attempt to match the load dimensionality observation or measurement to hide dimensionality observation.

So right now you show the data of IR release. I think that arm of drug absorption is compressed. That's why you can see a better correlation. But I think for modified release or extended release, that arm needs to be considered into the development of any IVIVC or IVIVR. Again, that's just a general comment.

DR. AMIDON: We have Dr. Sun and then

Dr. Smith.

Dr. Sun?

DR. SUN: One comment and one suggestion. One comment for Dr. Yu's slide 65. I think if everybody can see 65, Dr. Yu's presentation, it's my understanding here that that's a perfect illustration.

So the paper published by Dr. Janet Woodcock, Dr. Yu, and Dr. Khan in New England Journal of Medicine, we all know that story, the withdrawal of ibuprofen, one of the generic product. That paper and the news, it would be nice if you can have an in vitro dissolution to catch this before you come to this point, and after patient use, the patient complains there's no bioequivalence, the later form is not bioequivalent.

If in vitro testing captures, it would be really, really nice. The problem is I don't think currently there's a test you can catch this. So that's the number one problem. Now, that's why the full extended-release or modified release, the

IVIVR is so critical at this point. So I feel the IVIVR for this situation and the PBPK could link together. You cannot really separate those two independent things. Really, you do that, you model that. That's the ideal situation.

In this paper, I think you guys made assumptions -- made a suspicion, or maybe the generic is released too early. That's the only suspicion at that time that you have, but after later study, that's perhaps not true either. My impression right now, my hypothesis is because this drug no complete release in colon [indiscernible] or later GI track.

Do I have that data? I don't, but I feel from other recent study of published data, I more believe it's now complete releasing later in GI tract. Maybe that's more plausible than earlier release. There's early release for sure, but later may be the problem. The question is do we have in vitro testing to capture that? We don't? So that's the problem I see.

So really then, the idea is for this IVIVR I

feel is so critical, can we develop something to capture this? Then you can solve a lot of problems. So that's my comment.

My suggestion would be PBPK, this term, is very similar to the term biopharmaceutics. You talk to different people. They have a different definition. PBPK is the same. When PBPK got first introduced, it was get a PK of the animal model, all the tissue, and then you scale that in human. For traditional pharmacokinetics, that's the definition. There they are trained. There they are taught. There they're teaching students.

Now PBPK is extended to more GI. Now it's using pharmaceutical quality. I think the definition is changing, but I think for the whole community, my impression is people still use different definition for PBPK. So it's a good idea to maybe somehow consolidate this different definition and make sure everybody is understanding the same page. Otherwise, we may talk about different things.

DR. AMIDON: Should we go to Dr. Smith?

DR. SMITH: Paul Smith, University of Maryland, College Park. It appears to me that the discussion's been very useful, but I think that the proposal that we we're supposed to vote on is in a sense premature. What seems to be missing, although the speakers alluded to its importance, is the idea that we could combine some kind of mathematical or computational information to bolster the in vitro testing that could be done in the hope that it would then be possibly related accurately enough to what would happen in the system of a given patient.

I'm not sure -- and maybe people here can enlighten me -- whatever models exist for the dissolution of some product as it passes through the different stages of the digestive tract. I don't know whether there have been studies. There must have been. And it seems to me that the place to begin this project is by trying to get a better grasp on, to the extent possible, data on what happens in the human with perhaps harmless substances.

And surely these kinds of studies have been done, and only then can we start to talk about attempting to create standards.

I would feel, on the basis of that thought, that the question that's going to come before us is perhaps not the right question to be asking at this time.

DR. AMIDON: Okay. Dr. Yu?

DR. YU: Could I come back? You're absolutely right. In order to -- you have an in vitro dissolution, which we don't have a lot. We have a different apparatus, different media, different conditions. We have the pharmacokinetics; bioequivalent study, we have done a lot. What's lacking is the in vivo absorption part. We have a very limited understanding. We have some kind of understanding, but not sufficient enough to actually see what is going on. And there are not a lot of studies going on.

So we're hoping that when we ask those questions, we begin to encourage academia or industry to begin to have a better understanding in

those conditions or in vivo dissolution to facilitate eventual development of the in vivo/in vitro relationship, because as a regulatory agency, we cannot say, well, industry, please go do the study understanding in vivo absorption and in vivo dissolution because it's related, but it's not related to our quality standards setting.

So therefore, we ask a general question, but we recognize under this question, there's multiple information or data that I think academia, industry, and FDA together need to continue to have a further understanding and better understanding. So with this support from you, at least we begin to start to making progress; otherwise we're going to start where we are. We will have very limited progress as we've made for last 20 years.

DR. SMITH: But that doesn't support and an advice to establish because -- and fairly, we're years from being able to establish standards. Perhaps the proposal should be to investigate the possibility or some less

prescriptive term, although -- this is a side comment -- I don't like human focus either.

DR. YU: Thank you.

DR. AMIDON: Dr. Sun?

DR. SUN: To follow up with Dr. Smith's question, I totally agree with you for the point we do need to collect more human data in order to validate things. That's the part I really do agree. The part I have different opinion is that in terms of PBPK in this biopharmaceutical area, there's actually quite a lot of work already done and lost obviously 20 years.

So the currently used software, the GastroPlus Simcyp, actually is based on -- the foundation is the earlier PBPK model. So in a way, it is in use already. The whole industry's using it, FDA's using it, academia is using it. So this is not a starting point. It's already 20 years of work there, so there's some foundation.

The challenge, I agree with you, there's still a lack of human data to really truly validate. But the good thing is, even in that

foundation, those are all the software available for the whole industry and whole community to use. So really, I don't think it's premature. I think it's perhaps good timing. This is long overdue and needs to move forward. Otherwise, we're stuck for another 20 years.

I thought I had another point, but it slipped my mind. I will comment later.

DR. AMIDON: Yes, Dr. Finestone?

DR. FINESTONE: Sandra Finestone, consumer representative. I just have a question or a point of clarification. I'm looking at the objective here. The objective of developing an IVIVC is to establish a predictive mathematical model describing the relationship between an in vitro property and a relevant in vivo response. That's what I'm hearing in a nutshell. That's what you're asking.

I'm also hearing that that's not possible because we don't have that, except I think I just heard you say --

DR. YU: Let me quickly clarify. Actually,

that's another point. We do have in vivo data in the last five years from Europe and U.S. So we have some, but of course, especially for extended release, we don't have it yet. But we have other in vivo data. So we do have some reference already. Of course, you need more. That's what I remembered.

DR. FINESTONE: So now I'm understanding it more. So there is some data. It's just not enough to do what you're asking to do, which is an in vitro test could possibly replace the in vivo PK, which would do what I would hope what you're suggesting, which is to minimize the need for unnecessary human testing. That's certainly my objective to this.

So the testing is there. There's just not enough to do what you want to do. So the question is do we need more of the IVIVC testing or not? Is that what you want to have done? I guess I'm a little bit confused about also the objective that you're asking for.

DR. YU: Yes. We are seeking the support

from this committee to move in that direction, which is a batter in vivo/ in vitro relationship with the development of this arena because this has been here for the last 20 years. We're hoping we get advances in this area. Eventually, if we develop a methodology, if we have enough information in place, we're probably able to reduce future in vivo studies to benefit our patient in the end. But we need to have an initial investment in this arena.

DR. FINESTONE: So you're asking industry for more data to support this theory forward.

DR. YU: To a certain extent, yes.

DR. FINESTONE: Thank you.

DR. KOPCHA: Right. And with that, if I could just add -- this is Mike Kopcha. If I could just add to that as well, because the way the question is worded, should FDA establish patient-focused dissolution standards, if the answer to that is yes, what that implies then is that we need to generate that data.

So I don't think it's the wrong question.

What that question then does, or depending upon the answer to that question, will then drive what we need to do to get to that quality standard. So hopefully that kind of rounds that all out.

DR. AMIDON: We have no more names on the list here, but we do have a little bit of flexibility on our schedule. We've been going for quite a while, but I'd like to see if there any other questions, clarifying questions. And in particular, I recognize, I suppose first, those that maybe haven't had a chance to ask a question if they have any. Yes? Dr. Terzic, please?

DR. CARRICO: Sorry.

DR. AMIDON: I'm sorry. Wrong person.

DR. CARRICO: Jeff Carrico. Sorry. I'll answer to whatever you call me if you like. Really, just more of a statement than a summary at the end, and playing off of the comment that was just made.

The way that I am viewing this, and you can tell me if I'm correct, is that the question is more of a step towards what you're wanting to do

than an end product. So I think that's what's led to some of the discussion that we've had, is that, rightfully so, the way it is written, it's almost like that this we're voting on whether or not we're going to have this idea or this capability. But really what we're voting for today, in my opinion, is the step toward the availability or capability of what we're looking at here.

Is that correct?

DR. KOPCHA: Right. The way we define it is that we need to know, does the FDA need to establish these patient-focused dissolution quality standards. And if the answer to that is yes, then obviously we've got to take the steps to do the work to be able to get there because you just want to make sure that whatever work we're doing is driving towards setting those standards, but we need the feedback from this group to say, yes, you should be setting those standards, so do what you need to do.

Or the way we were thinking about it when we posed that question is if we got yes, that would

mean do the work, OPG, to get to those quality standards. We'd be able to establish those quality standards to support the research and additional work that we have to go through.

DR. CARRICO: Thank you for that.

DR. KOPCHA: So you are correct.

DR. CARRICO: And while I have the microphone, I'll sixth, or whatever, the idea to continue to clarify the use of the word "patient" as we move forward with this. I just didn't jump in with that one since it had been stated, but I think through enough of us, maybe that should be a point going forward, that if it caused enough of us to stumble on it, then you may get that from others.

DR. KOPCHA: Good point, fair enough, and point taken. If the group has recommendations, we'd appreciate that as well. So feel free to provide us with that either today or subsequent to this meeting.

DR. TERZIC: Since I brought up first the patient term --

(Laughter.)

DR. TERZIC: -- and since I have heard that our colleagues in the FDA would like to keep it, although my colleagues here are a little bit ambivalent, you may want to change the term "focused." You could use the other term that you're using a lot, which is relevant. You can use "patient" relevant that.

DR. KOPCHA: We've tried that, and the industry has come back to us and said, "You know what that means, Mike? That means now we've got to do all these clinical studies." And they said, no, that's not what we're implying.

We've tried other versions, and this is probably the most innocuous one, but apparently it doesn't seem to be as innocuous as we thought.

DR. TERZIC: I use the fact that I'm not a native English speaker to suggest --

(Laughter.)

DR. TERZIC: -- that. Keep on trying, includes the most benevolent than anything else.

The other term that you may want to consider

in the questions, dissolution appears too isolated. Our colleagues brought it back, dissolution and absorption. In other terms, the drug levels in the blood were also not viewed as maybe the true endpoint. Simply using the term "predictive," so in other words, the idea of establishing patient-relevant predictive standards, then you open up a little bit of horizon, and it's more preparative to what ultimately you want to do. So I suggest an earlier maybe stage at which you are. That will be it. Thank you.

DR. KOPCHA: Thanks for the suggestions.

DR. AMIDON: We have Dr. Cook and Dr. Awni on the list here, but I'm going to ask you if, if you have clarifying questions, you could ask. Otherwise, we'll have opportunity for discussion.

Is it good to hold off till discussion? Okay. It is now 3:00, so I propose a 10-minute break. So we'll pick back up at 3:10. Just as a reminder, no discussion of these issues amongst us or amongst any of the visitors in the room. There may be, again, a meeting going on next-door, so

just be aware of that. See you in 10 minutes.

(Whereupon, at 3:00 p.m., a recess was taken.)

Questions to the Committee and Discussion

DR. AMIDON: Okay. I think we're all reassembled here. There are no statements from the public as I understand it. So we will now proceed to the question to the committee based on our discussion that we've had. I would like to remind any public observers that while this meeting is open to the public for observation, public attendees may not participate except at the specific request of the committee.

So at this point I'd like to bring up the question to the committee and ask you to consider this, and see if there are any comments or questions concerning the wording of the question. So we're now open for discussion on this particular question that we'll be voting on.

Any comments or questions? Dr. Smith?

DR. SMITH: I'd like to suggest a rewording of the question. I would modify it as follows.

Should the FDA develop the scientific basis for establishing patient focused dissolution standards, et cetera, et cetera?

DR. AMIDON: I think we should consider the wording as it is and maybe be careful about wordsmithing it. I think -- and talking a little bit to others -- that we should discuss these questions and concerns we have, but vote on this, I would say, if it's acceptable, and have the opportunity then, if it's not, for clarifying comments and recommendations.

So does that make some sense? I want us not to go too far down the wordsmithing path on this, but points, concerns, pro and con, are important. So does that make some sense?

DR. SMITH: Sure.

DR. AMIDON: Dr. Polli, you want to add?

DR. POLLI: I think Dr. Smith raises a good point, and maybe I just read it differently. To me, I think I understand it. I mean, to your point, it's not like -- I don't think this question is suggesting that this be implemented tomorrow.

And then if the products don't show predictive CMA after they come off the market -- I interpret this exactly as maybe you've articulated it in your own mind, that it's more about putting things in place such that the numbers get better in terms of applicants actually having predictive dissolution models that do predict their, for example, pharmacokinetics, putting more incentives in place and things of that sort.

So to me, the question is actually pretty clear and similar to what you described.

DR. AMIDON: Good. Thank you. Dr. Sun?

DR. SUN: The same based on -- because six members raised the question of the patient. It seems that we have a split opinion on the patient. For pharmaceutical science, like my background, I did not read the concern you have. To me, I said this is very good. This is very personable [indiscernible]. I understand what you exactly mean, but to me, it did not cause -- misunderstanding patient means different disease population.

But I recognize when you guys with different background, you immediately -- something else comes to your mind is disease. I feel that's the situation. It depends who your audience is. For pharmaceutical science and dissolution scientists, I feel this is very good. I know exactly what you mean. So that's my comment.

DR. AMIDON: Dr. Mager?

DR. MAGER: I don't have a problem with it per se, but immediately when I read it, it just brought up those old arguments about we should be doing bioequivalent studies in patients, not healthy volunteers. And that's the first thing that popped into my head when I saw the word "patient focused," is that we are moving towards disease-specific predictions, and of course that's not where we're talking about.

DR. AMIDON: I had a comment, too. I suppose in some way, Drs. Smith and Polli, it touches on what you were saying. I looked at this and thought, to me this maybe doesn't go far enough. But again, I don't want to really

wordsmith it. But to me conveying how FDA and industry can proceed by advancing the application of computational, mechanistic, predictive, and biorelevant dissolution methods, to my way of thinking are the paths forward to achieving this.

So those are the thoughts that I had in reading this. To me, it doesn't necessarily clearly indicate the direction that one could go in doing this, but that's just my --

Dr. Sun?

DR. SUN: Quick, if we have to change -- I understand Dr. Smith's point. The wording you have, actually, I understand is the same way being tended to, but that to me is somewhat a wag [indiscernible] also. When I scientific basis, it's very broad in a sense.

If we have to change, another wording -- we don't have to change it. We can just put it -- establish a biorelevant dissolution, then there's no patient anymore. Then you go back to the old wording, "biorelevant." At least you don't cause confusion. So I guess I agree with you that

maybe we don't put it as -- whatever wording you use, put as a consideration without changing things right now for discussion.

DR. AMIDON: Good. Any other comments or concerns regarding the question at hand, that you'd like to bring up before we proceed to a vote? Dr. Donovan?

DR. DONOVAN: And I'm not suggesting wordsmithing, but I will tell you, the word that I'm uncomfortable with is actually "establish," because as I read this, it strikes -- if I were to read it when not having been listening to this discussion, it would look to me like FDA is going to make another regulatory standard, whereas, really, my understanding after the discussion is that FDA is interested in developing and working with people to establish oftentimes product-specific, patient-focused, in quotes, "dissolution standards."

So I at least want it on the record that right now as it reads, it strikes me that others might perceive it as the FDA is going to develop

their own regulatory standard regarding this. And I think as it's played, that it should be clear that FDA wants to partner and encourage the establishment and understanding of those methods.

DR. AMIDON: Good. Thank you. I actually had a concern about that, the word "established" as well for a slightly different reason. I think FDA in some ways has established, so to me it's more advancing or moving the science forward; a little bit different take but still same question about that word per se.

Anything else from anyone? Dr. Cook?

DR. COOK: Thank you. The chair recognized me. I've got one comment and then two comments that pertain to maybe helping out here. And the one comment is I understood where you're coming from. I guess I've been -- I won't say old -- experienced enough to be in where we're trying to establish it as something in process control a QC standard, or are we trying to assure bioequivalence? And seeing how those two never fit exactly right, I empathize with how we struggle.

A couple of things to consider. You've put the focus a little bit on ER, extended-release products. I actually think those are more rare in development, and we might be faster to also include class 2 compounds that are indeed highly permeable where dissolution is the rate driver, because I think we can learn a lot from those, and those are more common in development.

Then something that I struggle with a little bit at my company, and I'm trying to figure out how we can make this happen more, is that the idea of developing an IVIVC is not a one-study thing. And too many times -- especially if you use it on ER as a product extension. Now, I'm going to do one study. I'm going to develop it. I've got to have the dissolution test right and everything; oh, it didn't work out.

I've written a paper on this, that actually maybe what you should do is before you ever enter a drug and demand [indiscernible], you usually have a dissolution test. And usually a prediction of PK, you can actually test what you think the results

are and then adjust either the dissolution tests or the in vivo PK to reflect what goes on. And then in your next study, you can continue to do that.

Then finally, the IVIVC is actually a confirmatory trial if all works out that way. That's not the norm. Anything you could think of that to help promote that -- and I'll continue to try to promote that within. But there's so much of a learning opportunity during drug development that we don't take advantage of. And that's why I want to focus on class 2 compounds because I think they're the more often, and that's where we're going to learn, and that's where we're going to accelerate.

DR. AMIDON: Okay. Thank you. Any other comments?

(No response.)

DR. AMIDON: Seeing none, we can move on to the voting process. I will remind you of the voting process. We'll be using the electronic system again for this meeting. Once we begin the vote, the buttons will start flashing as you see

them on your microphone, and they will continue to flash after, even after you have entered your vote.

So please, when we tell you to, press the button firmly to acknowledge that corresponds to your vote. If you're unsure if your vote was registered or you want to change your vote, you can press the corresponding button until the vote is closed.

So after everyone has voted, the vote will be locked in, and the vote will then be displayed on the screen. The DFO will read the results of the vote for the record. Next then, we'll go around the room, and each individual who voted will state their name and their vote into the record. We've had great discussion this afternoon, so you can also state the reason you voted as you did if you want to, and you can add any clarifications to that. We've had a good deal of discussion on this topic.

So I think we're ready now to vote, so please enter your vote on this question.

(Voting.)

CDR SHEPHERD: For the record, the vote is 11, yes; zero, no; zero abstain.

DR. AMIDON: Good. Thank you. Now that the vote is complete, we're going to go around the room as I mentioned. Please state your name, how you voted, and the reason why you voted as you did into the record. We'll start over here on my right with Dr. Donovan and go around the room.

DR. DONOVAN: Maureen Donovan, University of Iowa. I voted yes. I strongly encourage this action. I think it contributes to our understanding of drug products and drug product action. And in the long run, we'll improve quality standards. So I think it's a win for everybody.

DR. SUN: Duxin Sun. I vote for yes. This is long overdue, and it's really can helped to improve the quality, can tell the different quality, which can show the difference in human.

DR. LI: Tonglei Li, Purdue University. My vote is yes, and I share the vision of FDA. And I truly believe this effort will promote and advance the pharmaceutical sciences, as well as regulatory

studies of pharmaceutic products. Thank you.

DR. FINESTONE: Sandra Finestone, consumer representative. I voted yes. It sounds to me, if my understanding is correct, that this will add to the body of information that will subsequently help patients.

DR. MAGER: Don Mager. I voted yes pretty much for the reasons that have been stated. I think it's long overdue, and the science is there. I think we can begin to move forward in that way. I would, again, highly encourage a model-informed approach with more advanced PBPK modeling approaches to improve predictability, and then to make that link that you were referring to, the IVIVC, such that those predictions can be then generated in an easier manner. And then, I agree with Dr. Cook that eventually these become confirmatory trials instead of exploratory trials.

DR. AMIDON: Greg Amidon. I voted yes. I agree with those sentiments already expressed that this is very much a do. I think this gives us an opportunity to have FDA and industry proceed

forward to advance the application of the tools that we've discussed here: computational tools, PKPD modeling in combination with predictive and biorelevant dissolution methods to advance our understanding of extended-release dosage forms.

DR. CARRICO: Jeff Carrico, NIH. I ted yes. think that the clarifications, qualifications, and discussions that we've had today are a great first step towards the achievement of this goal.

DR. TERZIC: Andre Terzic. I voted yes. This is a laudable effort by our FDA colleagues. It's a timely effort both from an unmet need that exists and also with the evolution of technology that will facilitate a science-based approach to this topic. I think the comments, as mentioned previously, during this session will help the FDA advance this topic rapidly forward.

DR. SLATTUM: Patty Slattum at Virginia Commonwealth University, and I voted yes for the reasons already expressed and the clarifications that came in the discussion today. The direction is clear and I think one that's laudable and we

should be doing. I think there are a few things that we can think about in the wording of how we describe it so that it's clear to all the stakeholders.

DR. SMITH: I'm Paul Smith from University of Maryland, College Park. I voted yes. There's no question that this would be a valuable scientific enterprise, and properly explained to the public, I believe that it's something that's going to have wide support.

DR. POLLI: James Polli, University of Maryland. I voted yes. I do like the term "patient focused." I understand it can have different meanings and different contexts, but I think to a lot of pharmaceutical scientists, it clearly points as being something different from QC testing, which we're all very familiar with.

I think there's a lot of confidence in QC testing, and QC testing does go towards therapeutic benefit, but I think it's also fair to say -- I would agree with this that we're probably overdue for this. Something like this will give greater

opportunity for development teams to invest in, needing to know about how their product performs.

I really kind of locked on to Dr. Seo's slide about it's seen as an all or nothing, and it certainly is. How many of us can stand next to our favorite dissolution apparatus and say I'm going to predict Cmax within 10 percent using this? And if I don't, if I fail -- I didn't see the word "fail," but I think Dr. Seo mentioned reluctance. There's certainly reluctance in standing next to a dissolution apparatus and saying you're going to predict Cmax within 10 percent.

So I think development teams need a little more help in terms of being encouraged to put more time into the quality question. I think they do that already, but encouraging that even a little bit more.

DR. AMIDON: Good. Thank you. Before we adjourn, are there any last comments from FDA?

DR. KOPCHA: Yes. I just want to take the opportunity to thank the panel for engaging in this discussion with us. It was a very good discussion.

A lot of good things came out of it, a lot of good recommendations, and we'll take those to heart as we read through the minutes of the meeting and make sure that we address those as we drive this further.

I know it's taken probably more than a day if you put it in the travel there for some of you, so I do appreciate the efforts and the interest and the desire to help us really drive this forward so that we can better serve the public in terms of the quality products we bring to market. So thank you.

I also want to thank the members of my OPQ team that actually helped put this together, this advisory committee. It required a lot of work and a lot of time to do that, so I want to thank my staff. Too numerous to do right here, but I do want to recognize their efforts as well. So again, thank you.

Adjournment

DR. AMIDON: Great. Thank you very much, and thanks to all of you for taking the time to come here as well.

Please take everything, all your personal belongings with you as you leave the room. All the materials that are left on the table will be disposed of, so just keep that in mind. I guess they are able to take along the materials that have been provided, if you wish. So you may take them if you wish, as I understand it.

Please remember to drop off your badge at the registration table, just right outside I think here, on your way out so that they can be recycled, and we will adjourn for the meeting. Thank you very much. Have a safe trip.

(Whereupon, at 3:33 p.m., the afternoon session was adjourned.)