FOOD AND DRUG ADMINISTRATION

Generic Drug User Fee Amendment of

2017 Regulatory Science Initiatives

Request for Public Input for

FY 2020 Generic Drug Research

Public Workshop

Wednesday, May 1, 2019

8:34 a.m. to 4:28 p.m.

FDA White Oak Campus

White Oak Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

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P R O C E E D I N G S

(8:34 a.m.)

Introduction - Robert Lionberger

DR. LIONBERGER: Good morning, everyone, and welcome to the 2019 Generic Drug Regulatory Science Public Workshop. I want to welcome both the attendees in the room and those of you who have joined us online through our process.

I'm Rob Lionberger. I'm the director of the Office of Research and Standards in the Office of Generic Drugs, and I'll be moderating the meeting today.

The purpose of our workshop is to seek input from various stakeholders on our regulatory science research priorities. This is something that FDA has committed to in the GDUFA negotiations, and it's in our commitment letter. It's been in our commitment letter in GDUFA I and continued into GDUFA II. So this is an important part of helping us identify what regulatory science activities will be of the highest impact to the generic drug program.

Today's workshop is divided into three main sessions. In the first session, we'll be talking about the implementation of our FY 19 priorities. These are improvements and optimizations of things related to priorities that are already on our lists.

In the afternoon, we'll turn our focus toward the future, first starting with a session looking at newly approved new drug applications. These are the basis of submission for future generic products, and we'll look at and have some discussion around those, identifying issues for potential future research.

Then we'll end with a session that's a little bit more open ended, looking at other research areas that aren't on our priority list, that may be important for the generic drug program in the future.

So we'll be listening to all the comments at the meeting. There will be a recording of this meeting. This meeting will be transcribed. There will be a transcript available. Certainly,

anything you say at this meeting will be captured and included in our consideration of the priorities.

But there's another way that you can contribute, and this is also very important. There's a public docket that's open. So we encourage people to submit written comments to the public docket. If there's something that you hear here that you think is important, please send that comment into the docket. During the discussion, I will remind you again, if you raise something important, also please bring that into the docket. That's important, so we'll look at that as well as we generate our priority list. I want to remind people of that.

There's also a process on the FR notice if you have some information. The docket is public. If there is confidential information that you think is relevant, so for example, you are a generic drug developer or needed a particular study, and you learned something, but it's not public information, there is a process in the FR notice for

confidential comments as well, and we welcome those as well, and we'll consider that.

So if there are things you think we should be aware of as we prioritize activities that are confidential, there's a process for that.

Before we begin the meeting, I want to go over some of the housekeeping rules for this meeting. First, please silence all your mobile phones. If you have not done so, please check in at the registration desk, and we'll be having breaks in the morning and the afternoon, 15-minute breaks, and then there will be a lunch hour around noontime.

I think this is the most important housekeeping information. If you want to have a lunch at lunchtime, you need to preorder your lunch. If you did not preorder your lunch before now, your last opportunity to preorder lunch is in the morning break. That's probably the most important housekeeping. If you'd like a lunch, go to the kiosk and preorder your lunch during the morning break.

The restrooms are located outside the main entrance, just in the back of the room in that direction. Again, the workshop is being record and a transcript will be available.

Lastly, we ask that people not interrupt the public comments, period, or the speakers, and we'll maintain order. All requests to make verbal comments will come to the moderator. So at my discretion, if the panelists feel they want to ask questions of members of the audience or speakers, then we will indicate and encourage you to come to the microphones there. So that will be at the discretion of the moderator for the members of the public to participate in the meeting.

Finally, I'd like to again just thank everyone for being here and participating. I look forward to a lively thoughtful discussion around these topics. To kick off the meeting, it's my great pleasure to introduce OGD's new office director, Dr. Sally Choe. She'll be giving the introductory remarks. This is the first time she's attended this workshop, so we want to give her a

very warm welcome.

(Applause.)

Opening Remarks - Sally Choe

DR. CHOE: start Thank you, Rob, and I'm glad you tested the microphone before I got here.

Good morning. Welcome to Generic Drug Research Public Workshop. Obviously, this is a very important workshop where we receive the public input for fiscal year 2020 science priorities.

As many of you are aware, Generic Drug User Fee Amendments, GDUFA, science and research supports innovative methodologies and efficient tools to establish drug product equivalence standards for generic drug development.

This, of course, includes the complex drug product development, which is quite challenging. Intensive FDA intramural and extramural research efforts, as well as cross-office or cross-center collaboration, have been undertaken to promote science related to generic drugs. Since the start of the GDUFA research program in fiscal year 2013, the Office of Generic Drugs has awarded over

130 grants and contracts and has established extensive collaborations with various FDA laboratories and offices.

These internal and external research activities have enabled development of product-specific guidances and timely review and assessment of a pre-ANDA meeting request, controlled correspondence, and ANDA applications.

As many of you are aware, actually, I have assumed the director position at Office of Generic Drugs about two months ago, and this is actually my first time actually attending this workshop, which is quite exciting.

One of the very attractive aspects of this OGD is that we have, actually, the opportunity to research and get some real answers that can impact the actual development, assessment, and subsequently the approval of generic drug products.

In FY 2018, there are more than 1,000 generic drug approvals and tentative approvals. First, generics made up nearly 10 percent of all approvals, of which 18 percent were complex generic

drugs. Of all generics approved, about 14 percent were for complex generic drugs.

These approvals were supported by significant achievements and advancements in our understanding of the science of equivalence through results from the GDUFA research program. In addition, OGD issued 245 new and revised product-specific guidances in FY 2018. Almost half of these product-specific guidances were for complex drug products.

While FY 2018 was the first year of the new GDUFA II commitment to pre-ANDA meetings for complex products, industry submitted 83 meeting requests, which actually almost tripled the meeting requests that we received in the previous year, in FY 2017.

FDA is able to provide substantive interactions and evaluation of innovative approaches because of the preparations that come from prior years of investments in the scientific area, related to the complex generics.

Earlier this year, FDA approved the first

generic Advair Diskus. This noteworthy approval was supported by at least 15 years of research conducted both internally in OGD and externally through OGD's collaborations with industry and academia.

As a matter of fact, I was an acting team leader at the Office of Clinical Pharmacology, supporting the Division of Pulmonary and Allergy Products at FDA in about 2010-2011 time period.

During that time, I had an opportunity to attend an orally inhaled drug product development workshop specifically focusing on how to evaluate the bioequivalence of these types of drug products, close by Bethesda, Maryland. At that workshop, I remember thinking what a challenge it is to actually develop a generic product in this area and thought it will take quite a bit of efforts and time to achieve one.

Well, after eight or nine years since then, now we actually have that generic product. This is an incredible and remarkable achievement.

The support through the GDUFA research

program has been critical in this effort, as research provided scientific knowledge for developing the product-specific guidance for this product and for preparing the response to the regulatory submissions.

FDA consults and solicits input from the public, industry, and academia to develop an annual list of a GDUFA regulatory science initiative specific to the research on generic drugs. Much of the public input for the yearly initiatives is obtained from today's workshop, including comments submitted to the public docket that Rob actually mentioned earlier.

We value the input that we receive from the public through this annual public workshop, which has been conducted each year since the start of the GDUFA program. The input from the representatives of the generic industry provides a valuable perspective about which potential research activities address current challenges in generic product development.

Looking at, actually, today's agenda, I was

quite excited that many of the topics actually do have some relevance to my past experience and background. As some of you might be aware, my graduate program advisor, Dr. Gordon Amidon at the University of Michigan, is the one who initiated the biopharmaceutics classification system, and I noticed that the BCS class III discussion will be happening by many speakers today.

Another topic, the prediction of the food effect; well, actually, my PhD dissertation was about the gastric emptying and the drug absorption along the GI tract.

Also, when I joined, actually, Pfizer, I was introduced to the modeling and simulation at the clinical pharmacology group, where I had great teachers and peers who were actually leaders in that area.

What you'll be presenting and hearing and discussing today here are exciting and important topics which will directly support achieving our office's mission of making high-quality affordable medicine available to the public.

I'd like to thank the presenters and panelists at today's workshop in providing valuable scientific input, also the organizing committee members who have worked really hard to make this workshop successful again for this year, and of course, all of you in the audience in your support of this important research effort. I hope that you really enjoy today's workshop and thank you.

(Applause.)

DR. LIONBERGER: I have just a few final introductory remarks before we get started. Just in the slides again, there's a record. Again, we want public input on our research priorities and there are various ways to do that.

In a reminder of the format, we have a morning panel focusing on our FY 2019 priorities. I want to say a little bit about why we chose these topics. I think everybody knows that complex generics are very important. We've heard a lot about them. But I think, in the past few years, we've really had a lot of focus on the priorities for complex generics.

We have very clear priorities for there. We've discussed these at our biannual meetings with the generic drug industry. We think we have strong alignment that our priorities on complex generics are aligned with industry needs, so we have a lot of clarity on that.

So this year, we decided to really explicitly focus a little bit more on some of the biopharmaceutics questions. That's why we have topics on the BCS and the fed bioequivalence specifically called out this year because those are areas that are on our priority list, but we really want to get more input from industry on what the most impactful things that we can do in those areas are.

In the context for this, certainly complex generics are very important. As Sally mentioned, about 14 percent of our approvals are complex generics. That means 86 percent are the noncomplex products, so we want to make sure that we are looking also at those products as well to make sure our research program is helping optimal development

in those areas.

In the afternoon, we'll come back to complex products as we look at new approvals and new areas of research, but I just want to give people that perspective on why we selected some of these topics for our initial discussion this morning.

Again, as Sally mentioned, the GDUFA research is critically important to our whole generic drug program. It helps inform all of our product-specific guidances. The new aspect in GDUFA II of the pre-ANDA meetings, we got about 90 requests in the first year.

The discussions at those meetings wouldn't be useful or fruitful without the scientific work that comes out of the priorities here. We discuss new approaches with applicants. We're really prepared, based on these research activities, to discuss them to bring in the best available science into that discussion. So from my perspective, it's clear this research is important to making our product development and review more efficient.

So with that, this workshop is focused on the future, but we've been working hard for the past six or seven years, so we have a lot of activity. If you want to hear more about the outcomes of the research, we won't just have time to talk about them today, so we encourage you to sign up for our September workshop, working with the CDER SBIA group for regulatory education for industry.

This is a two-day workshop, College Park, Maryland. Really, you'll hear details about deep dive into some of the research results and the linkage into our guidances and ANDA review processes. That's really about the outcomes of the research. This meeting is really focused on what are we going to be doing in the future.

So with that, I'd like to move to our first topic. In our first topic, we've framed some discussion around the BCS biowaivers, so we have great panel members. We have leadership of FDA's BCS committee on our panel. We have the FDA members who are participating in the ICH

harmonization on BCS on our panel for a great discussion here.

I also want to frame this as FDA has clear guidance on the BCS. The perspective here is where do we want to be in the future. What should the BCS process look like in five years from now? And in order to get there, we want to identify what types of research we want to be looking at.

This is not to sort of say a discussion really about our current guidance. It's really a discussion about what our future state should look at. As we go into the panel, we'll dig into that more.

To start the discussion, we'd like to ask our first speaker, Sid Bhoopathy from Absorption Systems, to give a perspective from people who are working on the submissions in this area, so welcome, Sid.

Presentation - Sid Bhoopathy

DR. BHOOPATHY: Good morning. I would like to thank the organizers for this invite. I'll be talking a little bit about how to study the impact

of excipients on BCS Class 3 drug product dissolution and permeability. Before I begin the conversation on how does one study this, I just want to take a small step back and talk about why this may be important.

One of the reasons we have gathered to have this conversation around is, is there value to our industry in expanding class 2 biowaivers to non-Q1/Q2 formulations? Now, one of the reasons this can be important is that a biowaiver is fairly certain. It is less predicated on the PK variability of the drug substance, which also means that this can be a great value proposition, maybe not cost as much, be faster to complete, and so on.

In addition to this, various authors have published on potentially the right applicability of drug products that have eligibility for a BCS 3 waiver. So there are multiple reasons why one would want to consider expanding this bucket of biowaiver eligibility.

Now, the reason this technique is more certain regardless of the PK variability is because

of the foundation. The foundation, the basis, is absorptive flux, which is a product of the concentration of the drug substance at the intestinal wall, combined with its effective permeability.

Essentially, if two drug products containing the same drug substance have the same concentration time profile at the intestinal membrane surface, i.e., have the same in vivo dissolution profile, then you'd expect them to be bioequivalent, which further implies that should there be tools that can demonstrate that the same GI concentration time profile does exist, then you have what is a reliable surrogate for judging equivalence of pharmaceutically equivalent drug products.

With that basis, the techniques to discern or to understand bioavailability are fairly straightforward; you are to establish that drug substance is highly soluble and that the drug product is rapidly dissolving. But because we're discussing BCS 3, and with the effect of the

permeability's load, absorption is incomplete, it is also a requirement for composition similarity. Lower effect of permeability means that there are a greater number of factors that can modulate the drug substance's permeability, so it becomes a more important consideration.

Composition similarity is written a few different ways. Here, I have language from the FDA guidance of December 2017 and also from the ICH draft from June 2018, but essentially, the paradigms are similar as in there are rules around -- or guidances around what may or may not be permissible.

ICH takes it one step further and makes a distinction between excipients that may affect absorption, that are known to affect absorption, placing tighter constraints on those versus the other larger set of excipients.

Now, with such constraints, of course, do come challenges. They can be made as forms. Challenges could be potentially legal. We receive feedback from the agency on confirmation of this

excipient environment, logistics, and how long does it take to obtain this feedback. Again, one of the earliest slides indicated that the value proposition of biowaiver is a speed to completion, and if you had to have this conversation, that can add to your overall development cycle. Then how good are the existing deformulation techniques? Can they achieve the constraints imposed, so to speak?

Always with challenges, there are potential solutions and ways to work around them. One school of thought would be can we create excipient exception categories that are wider? Do such tolerance limits have to apply to insoluble excipients that would not necessarily interact with this completely solubilized drug substance? What about excipients that are full constituents? Do we still need to be as much concerned about this?

The direction I'm taking here is that, essentially, you can map out these interactions because, yes, excipients may impact absorption, but the number of ways that excipients can impact

absorption are finite and can be thought through based on the drug substance and the question, and also the excipients that are specific to that solid oral dosage form.

This illustration is the progression of an immediate-release solid oral dosage form from product to drug in bloodstream. What is in red are the different areas of interaction. Again, not all of them will be on the same plane or hierarchy depending on the drug substance and the excipient composition for the product. There are ways one could maybe make a case that these matter more in this situation, and this is how we intend to study or demonstrate the lack of impact.

Here's where I want to spend a few minutes talking about what is next in terms of tools that are available to do this. Conventional techniques for dissolution would be some sort of a USP apparatus in conditions that are specific to the product, drug substance, and permeation, a host of available nonclinical intestinal permeation methodologies such as using cell monolayers, some

sort of an in situ profusion model, or maybe even using excised tissue.

There are many publications on this where these types of approaches have been used to understand the impact of excipients specifically on class 3 products. Some limitations that are able to garner along the way as we reviewed the publications; dissolution testing can be insensitive to excipient drug complexation, Caco-2 cell monolayers when you think about the conventional static model, which is the top and bottom approach, can be overly sensitive.

There are deviations from real-world correlation as more false-positives when you use such methodologies. Sometimes the model can have too much variability, making it difficult to discern the impact of an excipient.

Also, when you start thinking, can I run clinical studies to build out a case for certain excipients, some observations are that sometimes it is difficult to deconvolute the specific impact of an excipient versus everything else that is within

the product, and it's hard to scale or extrapolate the results of these in vivo studies.

Again, going back to what Rob just mentioned, biopharmaceutics, can that be used to develop tools that are more biorelevant? One such tool that we are now using more routinely is called IDAS, which is in vitro dissolution absorption system. It combines the dissolution result with inserts that have cell monolayers or excised tissue, but the idea is to not only study dissolution, but also at the same time quantify interactions with a biorelevant membrane.

A few applications that I'll illustrate along the way; on my left panel is the batch release data from product A, where the release is quite similar across the different manufacturers. But the problem presented was that the effect is not the same, that there were observations that not all of these manufacturers are working the same in the clinic.

Using these biopharmaceutics approach of combining dissolution and permeation, we did see

differences in the percent permeated, which is not as readily picked up with just the release.

The bottom panel is for a BCS class 3 drug product. Essentially, under all conditions, the testing RLD is super-imposable. The thinking here with IDAS is because you have a dual-gated process, you're able to slow things down, and maybe we will have picked up the failure in the clinical BE study if you had a more discriminatory approach.

Here's one more example. The left panel is amount dissolved over time, essentially indicating that when you look at the percent dissolved, there is no dose discrimination between the three different strengths; the 50, the 75, and the 100. But when you look at the percent permeated, concomitant evaluation using this methodology, because the drug substance is a substrate for intestinal reflux, which happens a lot with BCS 3, you're able to now see that there is dose discrimination when normalized to AUC.

There are a lot of resources, and I made this available. We're also thinking of new

experimentation and extension of previous work because the traditional Caco-2 can be overly sensitive, top-bottom. The geometry of the IDAS allows it maybe to have better in vivo correlation. Since you also have a dissolution component, you're not dumping excipients on top of a cell surface, which may result in a greater number of false positives.

That thinking here would be a finite conclusion such as a biowaiver cannot be granted. Can we start thinking exception categories, tools that are validated, and expanded tolerance ranges? Thank you.

(Applause.)

DR. LIONBERGER: Thank you very much.

Our next speaker is Siva Vaithiyalingam from Cipla. Welcome, Siva.

Presentation - Siva Vaithiyalingam

DR. VAITHIYALINGAM: Thank you, Rob and thank you for the organizers to have this meeting, and thanks for all the participants. I appreciate it.

We are going to talk about, in a nutshell, what is the requirement or what is the request from sponsors, industry sponsors, on the BCS class 3 drugs. Sid has covered great detail, and he has given a great framework for this session.

As of now, we have BCS class waivers for BCS molecules at molecules 1, and we are going to ask for this expansion towards BCS 3 molecules as well.

The framework for our question is to expand the scientific understanding of the role of excipients in generic drug products to support the expansion of BCS class 3 waivers to non-Q1 and non-Q2. Q1 is qualitative and Q2 is quantitative, sameness for the generic formulations to RLD.

The current guidance stands. As of now, it is the December 2017 guidance, and the definition for BCS class 3 is highly soluble and low permeable drug.

What are the requirements as of today for submitting an ANDA for BCS class 3 drug products? The current requirements are that drug substance

has to be highly soluble. The drug product, both test and orally, needs to be very rapidly dissolving. The critical point that we are interested in discussing today is, as of now, the agency requires the test formulation to be qualitatively the same and quantitatively very similar to orally.

As of now, it stands that agency has a requirement of one size fits all, where the agency is requesting, unlike BCS class 3 drugs, for a biowaiver to be scientifically justified. All the BCS class 3 test products must contain the same excipients as RLD.

Why is that a requirement? Because I believe the agency is concerned that the excipients can have a greater impact on the absorption of low permeability drugs, and the composition of the test product must be qualitatively the same, and it should be quantitatively very similar to RLD.

What is quantitatively very similar to RLD? This is exactly the slide that I have seen with Sid also. This is coming from SUPAC [ph] level 2

guidance. With this background, what we are proposing is to allow any justification for excipients that are qualitatively and quantitatively not similar.

How do we do the justification? The justification should be based on sponsor's prior knowledge and based on the scientific literature that the excipient has no impact on the absorption of the drugs.

Sid, thank you for that slide that you earlier showed that when the X are fixed to set off mechanisms by which the drug and excipients would interact in such a way that the excipient will have a limitation on the absorption of the drug.

Those are the scientific evidence and mechanistic understanding we would like to use for justifying why there shouldn't be a requirement for Q/Q sameness for BCS drugs. Of course, there are a lot of exceptions. For example, Mannitol comes to our mind where it can alter the absorption of the drugs by one or other means. Such excipients are required to be Q/Q between test and RLD.

In continuation of our ask, what we are suggesting is comparative physical chemical tests such as permeability on test and RLD could be developed to alleviate the concerns of quantitative differences in the drug product.

The transportation and the excipient transportation from a mechanistic point of view, all from empirical studies, available in the published literature could be used for justifying the non-Q/Q formulations.

Based on the broad evidences, what we found was many of the common excipients do not impact the permeability of the drugs in the GI tract, which sits well with what Sid has earlier said about the number of the proportion of the excipients that could impact the absorption of the drug.

We just independently did some literature search, and what we found out was there are quite a few literature available in the public domain that supports our hypothesis that most of the excipients do not impact the bioavailability of the drugs.

In this case, there are 12 excipients

studied under a few drugs, I think cimetidine and acyclovir, and what the researchers found was out of 14 excipients, 12 commonly available excipients did not impact the absorption of the drug. Similar results were found by the other authors as well on the BCS class 3 compounds.

There's another publication by this group of researchers where they used 3 BCS molecules; verapamil, propranolol, and atenolol, out of which they found that only one drug is considered for a biowaiver. Of course, there are some caveats in it.

There is another review article -- it's not a research article; it's a review article -- where the authors concluded extending the existing biowaiver to be granted for rapidly dissolving oral IR products containing class 3 API.

I'll give you one more example, a very similar outcome. Overall, the drug absorption, who is influenced substantially by an active transporter -- in such places where the excipient is an active transporter, there should be a caution

in selection of the excipient.

So there are some exceptions where we cannot have a blanket rule of all the excipients have no impact, but the scientific literature is suggesting that there are a good portion of excipients not impacting the absorption of the drug.

With this, our ask is to request the agency to spend on the research to figure out if there are any group of excipients or a list of excipients that will not have any impact on the absorption of the drugs. With that, I thank the panel and the audience for this opportunity.

(Applause.)

Panel Discussion

DR. LIONBERGER: So now, we will move to our panel session of the discussion. So I'd like to start with Ethan, who's sitting next -- if the panelists can please just quickly introduce themselves and their affiliation to start.

DR. STIER: Sure. My name is Ethan Stier. I'm the acting deputy office director for Office of

Bioequivalence.

DR. SHAW: Andrew Shaw, senior director of pharmacokinetics at Mylan Pharmaceuticals.

DR. SEO: Paul Seo, director of the Division of Biopharmaceutics and the Office of New Drug Products.

DR. RIEDMAIER: Arian Riedmaier, translational modeler at Abbvie.

DR. POLLI: James Polli. I'm a faculty member at the University of Maryland.

DR. NI: Zhanglin Ni, staff fellow, Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs.

DR. BHOOPATHY: Sid Bhoopathy, Absorption Systems.

DR. DeROSA: Gregg DeRosa, senior vice president at Teva.

DR. FREDO-KUMBARADZI: Emilija Fredo-Kumbaradzi, manager of biowaivers and biocorrelation, Apotex.

DR. KOZAK: Darby Kozak, team lead within the Division of Therapeutic Performance of Office

of Research and Standards in OGD.

DR. KIM: Myong-Jin Kim, deputy director, Division of Quantitative Methods and Modeling, Office of Research and Standards in OGD.

DR. MEHTA: Mehul Mehta, the outlier. I'm the division director of the Division of Clinical Pharmacology I in the Office of Clinical Pharmacology, New Drugs.

DR. LIONBERGER: I'd like to start this panel discussion by asking if there are any members of the panel that want to ask any questions of the speakers to clarify anything from their presentations. Mehul?

DR. MEHTA: Yes. This is just a clarifying question for Sid. One of the slides; you mentioned high solubility as the highest set dissolved, 250 milliliters. Well, we have realized that now, so it is a high single dose as the first option. And the second option is we can go down the highest set if there is additional information. So I just wanted to point that out.

I have one or two other questions, but

should I go with them or wait?

DR. LIONBERGER: I think any questions for the speaker, then we'll move on to a more general discussion. Any other questions? Jim?

DR. POLLI: Question for Sid. I'm not quite sure what slide it is, but it's entitled Why IDAS? And then you give an example drug. It's got green and white, and you give some percent permeation. I was just kind of wondering what the permeability of the drug was. Was it, like -- I guess it's low permeability, but was it very low? I'm trying to just understand the magnitude of the lowness of the drug.

DR. BHOOPATHY: Right.

DR. LIONBERGER: Closer into the microphone.

DR. BHOOPATHY: I will place it more in the low to moderate category, low to moderate category. It was not very low.

DR. LIONBERGER: Go ahead.

DR. FREDO-KUMBARADZI: Question for Sid; for the system IDAS that you spoke about, you are

speaking about biorelevant membrane, and here it's indicated like Caco monolayer. Can some other membranes be used as biorelevant beside the Caco layer?

DR. BHOOPATHY: Yes. We have also performed these studies with T-84 cells. We have not only looked at permeation endpoints. We've also looked at biomarker endpoints, where post-release, the drug substance is interacting with the membrane to elicit an response of maybe some set of cascade of events, so local GI. But the short answer is, yes.

We have also attempted to mount excise tissue. We have the most experience with Caco-2 cell monolayers, but definitely other biorelevant membranes.

DR. LIONBERGER: So Siva?

DR. VAITHIYALINGAM: I just have a question for Sid on the IDAS. Is there any experience you have on IDAS with any regulatory agency, just not FDA?

DR. BHOOPATHY: Yes, in Central America and

Latin America. We have performed some studies with the Panamanian authorities, with the Chilean authorities, as they're also asking very similar questions about impact of excipients and so on.

DR. LIONBERGER: Seeing no other clarifying questions, I'd like to open the panel for any comments that people have. And if you don't have any comments, I have a list of questions I'm going to start asking. So I think, Mehul, you had some discussion.

DR. MEHTA: I just wanted to pick on Sid a bit further in terms of his technical know-how. One of the slides -- I like the suggestion that says, "Can we get excipient exception categories?" For example, insoluble excipients, excipients that are food constituents?

I want to hear a bit more about that thought. Do you have any further suggestions of how that can be explored further?

DR. BHOOPATHY: Sure, Mehul. With insoluble excipients, which can also be a food constituent, I'm thinking, say, microcrystalline

cellulose, can we say that maybe up to the amount limit in the inactive ingredient database, it could be permissible because there is just a lower probability of this interacting of forming some kind of a complex with a completely solubilized drug substance. That's one that comes to mind. Lactose would be another one from a food constituent perspective, and along those lines, silicone dioxide, which is insoluble.

This is where I was thinking that two categories; since food is not many times limited with such drug products, your environment may be different depending on when you're administering a dose. And second, what is the prevalence of a completely insoluble excipient, interacting with a completely solubilized drug substance?

DR. MEHTA: So has anyone done like a systematic evaluation of this or made a proposal? If not, then maybe you should.

DR. BHOOPATHY: Yes. One part of this thinking is also borrowed from the new drug site. When you think about -- you know this, but when you

approach concomitant medication, it's primarily about the API potentially interacting with another API; transporters, metabolism, and so on. It's less about what are the excipient constituents in the other product, which may be impacting the drug substance permeation of absorption of the, say, primary API.

So clearly, there is some risk-based assessment that is being practiced. Can we borrow such principles?

DR. MEHTA: It's a good thought, but that will require a lot more discussion, how we do combination studies for the new drugs. Yes.

DR. LIONBERGER: I want to ask the industry reps a little bit about how much of a barrier really is the Q1/Q2 recommendation? Do you have examples where you say, I'd like to do a BCS waiver, but I really have to do a non-Q1/Q2. Say a little bit about the reasons why you might choose or feel obligated to have a non-Q1/Q2 formulation as part of your generic drug development.

DR. VAITHIYALINGAM: Rob, I'll take the

question. One is mainly on the IP constraints. It already has a patent on excipients. And not only just excipients. Sometimes they have a patent on how much is used, so that is one reason.

Second, lately it has become very cyclical to get a confirmation on Q/Q approach. It takes a pretty long time on multiple control correspondence, and each correspondence takes months. Those are the two things that come to my mind.

DR. LIONBERGER: Any other industry comments on the reasons why?

DR. VAITHIYALINGAM: Emilija, you want to talk about it?

DR. FREDO-KUMBARADZI: Yes. With Q1/Q2, challenges are typically around the compounds which are present at a low amount in the reference product formulation, and that makes deformulation and determination of the level accurately a big challenge.

Therefore, we end up filing control correspondence, and we get an answer, let's say,

that it's not good enough, but not what is not good enough in it, which leads us to -- obviously, time is critical for us as well, and that goes into several sequences of several rounds of filing control correspondence.

In particular, if we know that certain excipients are non-functional -- I'll just take an example, film coating. Is that really critical to be matched within the levels which are provided in the guidance document?

So that is the challenge. The analytical part is a challenge because you are analyzing a composition which is complex with multiple ingredients.

DR. VAITHIYALINGAM: Rob, I want to add one more thing. For instance, there are non-exception excipients that has to be Q/Q, or in parenterals; just an example of how this whole thing about Q/Q becomes so challenging?

Occasionally, there are instances where we wouldn't even know that an excipient is there in the innovative product. Based on the list of

excipients we see in the RLD package insert that is published on the FDA website, we think there are only 5 excipients.

But to our surprise, there is another excipient, which you wouldn't know it is there in the formulation until we got this multiple cycle. Then we realize we kept getting the answer it is non-Q/Q because it is not that we are non-Q/Q for the known excipients, but those unknown excipients, which are not listed, but the agency knows it.

DR. LIONBERGER: So were you able to figure out where those unknown excipients came from?

DR. VAITHIYALINGAM: In one example, it was a pH modifier, which was unknown.

DR. LIONBERGER: Not listed in the label?

DR. VAITHIYALINGAM: Exactly.

DR. LIONBERGER: Jim?

DR. POLLI: I have a question for Siva. Looking at your slide, I think it's probably around the ninth slide, where you talk about an alternative proposed risk-based approach. Everyone wants certainty.

How do you think a community should go about assessing whether --

DR. LIONBERGER: Jim, could you speak into the mic?

DR. POLLI: Sorry. How do you think a community should go about assessing -- let's just hypothesize that there's an excipient that has no effect on drug absorption. How can a community go about identifying that? What process would be good to do that? I do suspect there are excipients like that.

DR. VAITHIYALINGAM: So your question is how do you figure out a given excipient has no impact on --

DR. POLLI: If I can just interject, I realize there's always uncertainty about doing an experiment and then interpreting to what extent that applies to other drugs or other scenarios.

DR. VAITHIYALINGAM: I mean, this is a start, right? We are at the very initial phase of extending the BCS 1 to BCS 3. At this point, I really don't have a clear answer, but my thinking

is, it is both mechanistic and empirical.

If you look at how Sid presented in his slide deck, he clearly alluded that there are only certain days in which the interaction could happen, so we should map out first based on the API characteristics and the excipient characteristics, and then go from there, from a mechanistic point of view, and if there are any empirical experiments that need to be done, one has to do.

I'm not saying that at this point, we should just list the excipients, saying they are not going to impact. All I am saying is, we should take each situation in isolation and see how the given molecule absorption is impacted by a given set of excipients instead of just having a rule-based requirement of it has to be Q/Q. That's all. Thank you, James.

DR. FREDO-KUMBARADZI: If I can just add to what Siva said, there is literature evidence so far based on in vitro, some on in vivo studies, for impact or lack of impact of certain excipient on absorption using various BCS 3 model drugs.

We all know that surfactants, polyethylene glycol, or osmotic agents are those of concern, and we are not bringing those type of excipients, which are well known and confirmed, to this discussion.

In fact, in immediate-release products, those excipients are not needed. Drugs are highly soluble. So we are talking about common excipients, which if we put a list of common excipients, it won't be very long.

What we are looking into is to start with some smaller list, which will be eventually developed based on literature, based on experiments, and this is why we are raising this issue with the agencies, because we are looking into solution, how to prove that they do not have impact on permeability, not just to say, okay; these so far are not documented as such and they are good to go.

So we are looking for FDA to eventually support some sort of research to better characterize to begin with, with a smaller group of excipients. And over time, that may grow as

scientific evidence is accumulated. This will be of great help as a starting point, and that can be a joint effort between the agency, academia, and industry. Thank you.

DR. VAITHIYALINGAM: Thank you, Emilija. That's a good answer to my question.

DR. KIM: My question is related to those two comments that we are talking about here=. From the slide deck, Siva's slide deck, the alternate approach, the one thing -- or actually two things that kind of caught my eyes; one is about sponsor's prior knowledge and the second one, the literature based.

My question is for the industry. Have you ever considered maybe some sort of a joint effort amongst the sponsors to come up as your own list because I understand that you're asking the FDA to do some research and come up with a short list or whichever. Any thoughts on that from your end?

DR. VAITHIYALINGAM: As of now, we don't have that. Our common forum is GPHA/AAM. That's the only place where we meet. From a science point

of view, we have smaller groups under the AAM umbrella. It could be something that we could think about it. But I think, since this whole discussion is on the GDUFA science research initiatives, we thought of presenting this idea to the agency for their consideration.

DR. KIM: Sure.

DR. VAITHIYALINGAM: Thank you.

Emilija, you want to add something?

DR. FREDO-KUMBARADZI: Yes. From current experience, when we were actually performing a bioequivalent study with BCS 3 drugs, and the formulation of generic was not qualitatively -- not quantitatively, obviously -- similar to the reference. We have many examples of successful biostudies which indirectly actually thought that the difference in the excipients, whatever it was in that case, didn't play a role.

What we are looking at here is a more systematic approach because we need to pay attention to the level as well, not just whether it was present or not. Therefore, we are bringing it

for discussion and more systematic approach to that, but examples are there, multiple, where non-Q1/Q2 passed biostudy on target with no issues.

DR. LIONBERGER: Gregg?

DR. DeROSA: I was just going to say almost the exact same thing. I'm sure FDA has hundreds of examples of BCS class 3 products that are on the market today that have passed biostudy that are not Q1/Q2. Maybe, as an industry and as FDA, we could work together to figure that out. I mean, I'm sure a lot of these answers already are within our databases.

DR. LIONBERGER: Sid?

DR. BHOOPATHY: One other experience that we have from before is -- this is from Siva's slide deck, page 13. This publication was one of those types of joint efforts. Pfizer, GSK, FDA was involved. PQRI was the primary driver. But that was also many years ago, so a tendency for false positives, not having available correlation. The study was scaled back even though it was much more ambitious to begin with. But now, with, again,

better science, new tools, there is the chance to advance this.

DR. LIONBERGER: We've heard a lot from the industry about the Q1/Q2 part of the BCS class 3 waiver. I'd just like to ask the industry members about the rapid dissolution side of the BCS class 3 waivers.

Are there any examples where you looked at the dissolution data and determined that the BCS waiver -- like for example, you tested the RLD dissolution rate and the RLD took 20 minutes to dissolve. So has the dissolution aspect of FDA's current BCS class 3 recommendations had any impact on your decision to approach a BCS class 3 waiver?

I think, in general, the guidance asks for multimedia dissolution. Generally, for most immediate-release products, companies generally only do one dissolution. I don't know how many of those products actually meet that 15 minutes in the full multimedia set. But I'd like the industry perspective. Are there cases where the dissolution has been a factor in your decision to move -- has

been or would be a factor in the BCS class 3 case?

From your perspective, is the Q1/Q2 the more important issue, or is dissolution also an issue, or is Q1/Q2 more important than dissolution? I'd like to hear from the industry perspective on that.

DR. VAITHIYALINGAM: More often than not, it is the Q/Q. I'm not able to -- Emilija, you can jump in any time you want, but I don't see a situation, that at least I faced, where the dissolution is the bottom.

DR. FREDO-KUMBARADZI: With the current requirement of very rapid dissolution, this question is kind of addressed because, if both RLD and generic truly are very rapidly dissolving, then solubility factor is off the table because they will both become solution very quickly, and then permeability is the only concern, and this is where we are talking about whether excipients would impact that or not.

Some literature is actually saying that they are even better candidates because dissolution

is not the rate-limiting step, but rather the permeation, which means there would be examples, but I don't have this information off head, but it may be that, actually, even the slower dissolution then very rapid may not be that big of a concern considering that absorption is the rate-limiting step for these type of drugs.

DR. LIONBERGER: So the industry panel is telling us that you don't see very many cases where you have BCS class 3 drugs in formulations that take longer than 15 minutes to dissolve.

DR. FREDO-KUMBARADZI: Yes, majority.

DR. LIONBERGER: So that's not been an implementation issue or determinant issue for the future.

DR. FREDO-KUMBARADZI: Yes. But it is, again, an additional factor that can be looked into. Maybe even some simulations can be done on them instead.

DR. LIONBERGER: But in order to figure out whether this is our priority, we'd like to hear, if you say, "Oh. There are a lot of cases where we're

not pursuing them because the products are a little bit faster than that." But if that's not a factor that's impacted industry, that's what we're really asking here.

DR. FREDO-KUMBARADZI: Q1/Q2 is our major problem.

DR. VAITHIYALINGAM: Rob, also remember, this whole dissolution is just not the factor of API alone; it is a formulation. If I compress the tablet very hard, then that can slow down the dissolution.

You see what I'm saying? It's a property of the formulation as well. The dissolution is something, a soluble issue, within the industry's role, whereas Q/Q is --

DR. LIONBERGER: But I'm talking about the reference product dissolution rate. What if you had a reference product dissolution rate that takes 20 minutes? Is that a barrier to your use of a BCS class 3 waiver? That's not under your control. I mean, certainly, your product you can formulate to make it dissolve very rapidly.

DR. VAITHIYALINGAM: That's a good point. I remember it vaguely. There was one product where we had this challenge. The FDA was okay with that, the reference part being not within 15 minutes requirement. But yet, the test product was within 15 minutes, so I believe agency was okay with that justification, and we moved on with the busiest biowaiver requirements.

DR. KOZAK: I have a sort of general question in terms of we talked a little bit about going to this idea of being able to be non-Q1/Q2 and type of the excipients there. But is there a general agreement that the current in vitro tests and the analytical methods for that -- I think we heard a bit about the IDAS system.

Are those sufficient now to support that type of actual approach, or do you think that there needs to be greater development in that stage or validation in that stage, really, to have that uptake by the agency? Is there a research need there that we need to look at?

DR. SEO: I'll make a comment to that. I

think, when the BCS, the newer one, came out, extending BCS waivers class 3, one of the global arguments I hear right now, in this room especially, is, are we being too restrictive?

As regulators, we don't know what we don't know. Although the BCS framework is quite robust, there are things that we can't measure, for example GI motility and things of that nature. So we can't capture that. So there is a certain level of constraint that we would like to see to be sure.

There's a high risk to the patient for getting it wrong, whether it comes to safety or efficacy. So there is that component.

Whether we can expand the Q1/Q2 requirement, a lot of people think FDA is this huge organization. We are, and we have money to throw around, maybe. Then it comes to, you guys have all the data or we have a lot of data, but we don't have all the databases ready.

So what we would have to do is a brute force method. Unless we invest in AI, narrow AI, machine learning, that kind of thing, we would have

to throw some people into a basement. Let them come out over the weekend and see what they have to get that kind of information. It's not readily available to us.

There is a possibility in the future that we might have a list of excipients where we know that we're very comfortable with, but we're not quite there yet. Is that something that we can invest in? Probably.

One specific point I did want to address is the Q1/Q2 piece. That was a point of concern for a lot of regulators, I think, when we were discussing this at ICH. But I will say that our labs here at CDER, they did a deformulation study. What I can say about it is it was done pretty much from inception to finish in about 3 to 4 months with very minimal experience. They threw everything they had at it with regards to analytical techniques and methods.

We blinded them, and it was a good study. They were actually able to come up with a Q1/Q2 assessment pretty quickly and accurately. And

according to our labs, if they had more time and more experience with doing this, they would know in the future which analytical methods and techniques to use for certain kinds of excipients. Their indication to me was they would get more accurate and better at it with time.

I guess, Rob, to your point also with regards to what's a more limiting factor, Q1/Q2 or the very rapidly dissolving component, when I have meetings with big pharma, generally, the tendency is it's harder for them to meet the very rapidly dissolving component versus the Q1/Q2 component. So that's all.

DR. LIONBERGER: We are reaching the end of our discussion on the BCS class. This is your last opportunity to comment. Jim?

DR. POLLI: I guess I'll frame it as a question to Sid. I asked you a question earlier about what type of low permeability drug was it, and you said it was moderate. So I kind of think the same way. Low permeability in a sense just means it's not hot, but we know there are big

differences within low.

Do you have any experience where excipient effects, say, don't affect moderate low permeability but do affect low-low permeability? Dr. Seo mentioned risk assessment. Is there any risk assessment to be considered in thinking a little more specifically about this range from 0 to 85 percent?

DR. BHOOPATHY: The short answer is yes. I cannot remember the name off the top of my head, but there are -- the low moderate, say between 60 and 84 percent fraction absorbed, which look less like the acyclovirs and the nadolols, but look more like the minoxidils and such. There, the impact of the excipient is much more mitigated.

So one of the thoughts that we have contemplated internally is almost the latter, where if you have a validated system and apparent permeability is beyond a certain number, not high permeability in terms of standard threshold, but a number where you're able to say that it is now almost unlikely. That's a distinction between the

low-low versus the low-moderate, but that is how I think it would play out. So I would agree with the comment.

DR. LIONBERGER: We have to move on to our next topic. We'll move on to a discussion around fed bioequivalence studies. Again, this is a similar type topic. FDA has clear guidance on this, and the real question is what should the future state look like in this area again.

So we'll start off our discussion. We have some speakers with different perspectives, so our first speaker will be Arian Riedmaier from Abbvie.

Presentation - Arian Riedmaier

DR. RIEDMAIER: Thank you.

Good morning, everyone. I am going to take a different perspective now and talk about prediction of food effects in terms of modeling and simulation.

Just to give you a better background, R&D has been moving much more towards complex and hard-to-treat diseases, and this is resulting in lower tolerance, safety, and drug interaction risk,

especially for indications where we already have safe drugs in the market.

Novel opportunities in industry are moving the oral druggable space beyond the rule of 5. On this pie chart, you can see the BCS classification of approved drugs between 2011 to 2015, and you can see that more than half of the BCS-classified drugs in the market are BCS class 2, followed very closely by BCS class 3 and 4.

On the other plot, you can see the solubility distribution of the top 200 oral drugs marketed in the U.S., and you can see the top portion of that figure are showing that the majority of these compounds in the market are considered practically insoluble or sparingly soluble.

This has resulted in approximately 50 percent of approved drugs between the years of 2011 and 2015 utilizing either salt or a complex formulation approach. Of course, this opens up a really novel opportunity in terms of modeling and simulation as well, where we need to capture these

kinds of mechanisms and formulations.

In terms of impact of food effect on drug development, due to the changes of the GI physiology and the presence of food, absorption of orally administered drugs can be affected when they're taken with a meal, so food effect and bioavailability studies need to be conducted, and these are usually conducted to support NDAs for label recommendations.

However, food effect studies and the understanding of food effect really starts much earlier on at the preclinical stage at early discovery and development, where we're using two different approaches. So we're using studies in preclinical species, and I'm not going to get too much into that, but there is also a lot of discussion going on in terms of what species may be representative.

But at the same time, we're looking at in vitro biopharmaceutics approaches and modeling the results of these approaches to predict food effect. So we will have a prediction of a food

effect going into clinical developments before the clinical food effect in phase 1. Once we have the results from the clinical food effect at phase 1, we can then verify the model using the food effect studies. And once the model is verified, we then want to extrapolate that to novel formulations and special populations.

The reason why we have the preference to use these modeling approaches is because of the complex nature of food effect. We really need an integrated approach. Physiologically based absorption models have really emerged as a key platform to support food effect prediction because one single approach doesn't seem to be sufficient to really explain all the mechanisms that are ongoing, and we need to really use the integrated physiological, anatomical, pharmacokinetic and biopharmaceutics approach, and bring those all together in order to really understand what kind of food effect we might be expecting.

Of course, there has been a lot of different views in terms of prediction of food

effect from an industry perspective and a regulatory perspective. Various publications from industry, including an IQ paper that was published in 2015, have demonstrated that there is high to moderate confidence for predicting food effect of compounds with the exception of those that are transported, actively transported.

Publications from the FDA based on retrospective analysis don't share the same confidence necessarily and the bottom line is that we are not there yet. A recent FDA guidance on food effect suggests the possibility of considering BCS category, specifically BCS category 1 waiver, of food studies.

While this is really great, BCS classifications can serve as generalizations of drug property. However, the suggestion here is that appropriately verified physiologically relevant models can provide an even more powerful assessment of drug properties in combination with PK and physiological considerations. So if we're looking at it from a mechanistic perspective, we

can move away from the rule-based approach and we can look at the mechanism-based approach.

To give you an example of that, I want to go into the venetoclax case study. Venetoclax is a selective and orally bioavailable B-cell lymphoma-2 inhibitor that was developed for the treatment of chronic lymphocytic leukemia and other hematological illnesses.

Venetoclax is, by all definitions, a very complex compound. It's a BCS class 4. It's very large. It's lipophilic. It is highly protein bound, with an fuP of 1.3 times 10 to the power of negative 5. And it poses very large challenges to mechanistic modeling and formulation, as you can imagine.

For BCS class 4 compounds, there is a tendency for the application of solubility enabling formulations to enhance in vivo exposure. In the case of venetoclax, we used amorphous solid dispersion, or ASD, because we thought that it offered significant advantages over the crystalline formulation.

In addition, there is a tendency for high-molecular-weightdrugs to be slow crystallizers, which means that they can remain in the super saturated state, and this is another thing that we had to take into account for venetoclax.

In terms of what additional things we looked at for the model, venetoclax undergoes initial rapid supersaturation to its amorphous solubility, which occurs at 4.6 micrograms per mL. Above this concentration, drug-rich particles form and they replenish the amorphous drug to maintain concentrations at this amorphous solubility.

Within the model, we had to look at some of these key assumptions based on the in vitro data that were generated within human biorelevant conditions. And that's very relevant for this compound, that the conditions had to be biorelevant and that's what had to be fed into the model.

We ended up using the amorphous solubility that was measured in buffer instead of the crystalline solubility. The dissolution kinetics that was defined in the model allowed

supersaturation to be reached at the amorphous concentration, and then precipitation remained minimal after that point because of the point that I mentioned in the last slide.

We then predicted the concentration along the GI tract, but we verified them with measured concentrations in simulated GI fluid using pH dilution method. So again, this is a verified approach using in vitro data.

This is the outcome of those predictions. On your left, you can see the concentration time profile in the fasted state, so this is the first verification to make sure that we are capturing the fasted state correctly. On the table below, you can see how the predictions performed.

You can see that the prediction was verified. After that, we could go and look at the fed state, and again, you can see the fed state was verified very nicely as well. The bioavailability actually ended up being very close to the observed absolute bioavailability for this compound, so the predicted was 6 percent, and the absolute

bioavailability that was measured was 5.4.

You can see that the model performed really beautifully in this case. The message that I'm trying to get across here is that this is a BCS 4 compound, so with a generalization, we would have said we would have no confidence with BCS 4 compound. But again, once we do the modeling and we take into account the mechanism and all of the major data, we were able to capture the food effect very nicely.

So it's really a case-by-case scenario of looking at the mechanism and looking at what kind of confidence we have in terms of modeling these specific mechanisms rather than a single rule that would apply to everything.

I'm going to briefly touch on the 2018 IQ food effect working group. The reason why I want to touch on this is because a lot of the previous work that has gone into food effect prediction and our confidence around food effect prediction has been a retrospective approach.

While there's a lot of value to a

retrospective approach, what they do not account for is how the method was defined, how the experiments were conducted, how the modeling was conducted, and established workflow around the modeling work and in vitro measurements, and also the experience of the modeler is not taken into account.

So in terms of this IQ food effect working group, what we're trying to achieve is to use a consistent prospective approach, which is very different from what has been done in the past. In this case, we're bringing together a team of cross-functional modelers and formulation scientists from various pharmaceutical companies to establish a consistent workflow for modeling with standardized input data.

We want to agree upon principles and decision trees for data generation methodology, and we want to define how to appropriately verify these models before food effect prediction and a recommendation.

The vision for this group is that

conducting a published verification study of food effect prediction using PBPK can aid in understanding model of applications when it's done in the correct way. So we really want to define our confidence around what that correct way may be.

This is the timeline for the food effect working group. I'm not going to go into it, but it's just to say that we are sticking with the timeline, and at the moment, we're in the process of evaluating the outcomes.

Just to summarize, a mechanistic physiology based pharmacokinetic model can provide an exciting opportunity to utilize an integrated approach for understanding food effect in humans. The proposal to increase our confidence of these models is to apply a consistent workflow with standardized inputs to define a common strategy based on verified models and to come up with a cross-industry recommendation in terms of best practice based on a prospective approach rather than a retrospective approach.

Where models have been verified with

clinical food effect data, there are opportunities to utilize PBPK models in understanding food effect in the following cases. And with that, I'd like to thank everyone, and any questions?

(Applause.)

DR. LIONBERGER: Thank you, Arian. We will have questions in the panel discussion.

Our next speaker is Amitava Mitra from Sandoz, for the generic industry perspective on the food effect and fed BE studies.

Presentation - Amitava Mitra

DR. MITRA: Thanks, Rob, and thanks, Rob and Stephanie, for having me here today. I appreciate it very much.

Arian did a really nice job introducing PBPK and food effect predictions. This is just my disclaimer. These are my opinions, my opinions only.

I'm going to bring us back to BCS. Every one of you in the room probably has seen this in some shape or form on how food affects PK for the BCS 1, 2, 3, 4 molecules, so we all know this.

I'm going to try to build a case here today that if we understand -- if we have a good understanding of what is causing the food effect, the mechanism of a food effect, irrespective of the BCS class, we should be able to predict it with fairly good confidence. There are some "low-hanging fruit" quote/unquote, that are ready for us to be plugged, but we have not for some reason or another.

With that notion, if we look at, again, across the BCS classes, generally, why do we see food effect across these classes? Again, I'm sure everyone in this room knows this, but still, I'm going to try to preach to the choir here.

BCS 1 mostly delayed gastric emptying, which causes a delay in Tmax primarily. BCS 2 increased solubility and delayed gastric emptying. BCS 3, same thing; maybe there is some transporter involvement there, interaction with food components, et cetera, which might complicate prediction a little bit more. In BCS 4, I'm going to leave it alone for today because I don't think

we are there yet, although Arian made a very nice case with venetoclax, but I think it's a little bit more challenging, at least from my perspective.

The point is, if we understand with fair confidence for the molecule, whatever molecule we're working on, on what is causing the food effect, be it BCS 1, 2 -- I'm going to focus primarily on BCS 1 and 2, but I think we can extend the same argument to BCS 3's, too, within certain constraints.

Should we be able to or are we able to predict food effect or outcomes of fed BE studies? My argument is, yes, we are. And it is just not my perspective. If you look at the literature, based on our experience, with prediction of food effect using PBPK, within certain constraints for BCS 1's and BCS 2's, we have been able to predict food effect with fairly good confidence in a majority of the cases.

The reason is because the PBPK models in the last decade or so have evolved where the GI mechanisms are not a black box anymore. A lot of

these features are understood, there is data, and they are encoded in these PBPK models. It doesn't matter which software is the choice that you use.

Having said that, I'm going to put across to you certain constraints where I think we are, again, able to predict food effect fairly confidently. Again, I would request the regulators to look into it and do some research, and put them in the guidances, so the guidances are flexible enough for sponsors to be useful in a waiver of these fed studies, either just food effect or fed BE studies.

So where are we with this? So BCS 1's and 2's, again, a majority of the BCS 1 and 2 molecules, unless it's a very high first-pass metabolic compound which goes a very high first-pass metabolism, we know with fair confidence that it's a gastric emptying and solubility dissolution enhancement which affects food effect.

I would make the same argument for certain BCS class 3 molecules, too, unless we know for a fact that there is an interaction with excipients

or food that is causing certain challenges in absorption that we would not be able to predict with PBPK.

Compounds with linear PK or nonlinear PK, i.e., where there is the saturation of absorption primarily because of solubility, we should be able to predict these compounds fairly well for BCS 1's and 2's, and we know that there is no interaction of food with either good enzymes or with certain transporters.

Moderate to high bioavailability; again, I make the case for moderate to high bioavailability because if the bioavailability is low, there could be challenges. But within the constraints of moderate to high bioavailability across the compounds that we had worked on, or if we look at the literature, there is, again, fairly high confidence in prediction of food effect if in fasted state the bioavailability is at least moderate.

Reliable solubility and dissolution data; I think there was some discussion about this in the

BCS 3 biowaiver panel discussion. Obviously, the main premise here is the food effect is changing because of solubility and dissolution changes. With food, we need to have good confidence in those measurements of solubility and dissolution because that's one of the key inputs that goes into these PBPK models.

Reliable estimates of human PK parameters; there has been a lot of discussion in various forums and also in publications of bottoms-up prediction of PBPK. That is all fair and good, but again, at least from my perspective, I don't think we are there yet, at least from PBPK, to be able to predict, in a large number of cases, fully bottoms-up.

So, this is where the need to have a fair, good estimate of human PK, either from IV data or even oral data, Pop PK, whatever the source says, is having fair, good estimates of human PK parameters.

Obviously, we do need clinical data in at least one prandial state. Most likely, it will be

a fasted state, but for the model verification, we do need that. If you have fed state data, that obviously makes the model verification much easier to be able to predict the next food effect study.

Going back to a generic industry perspective, to be able to predict fed BE studies, obviously we need the intrasubject CVs for the PK parameters. And again, for most of these molecules, that is available from previous PK data.

The argument that I'm making here is, within these constraints for BCS 1, 2, and maybe certain BCS 3 molecules, if we have these datasets, we are able to predict food effect. And I would even argue that within these constraints, running fed BE studies, it's not necessary.

Again, I would urge the regulators to look into it. There is plenty of publications out there, maybe do some more research, and make the guidance's flexible enough that within certain constraints, the sponsors are able to waive food studies.

Even the recent 2019 draft food effect

guidance, even for BCS class 1 molecules, I did not think went far enough from a waiver perspective. Even everything that we know right now, even the BCS class 1's look like kind of a gray zone to me. You would make the same argument for the broad specific guidance's.

Again, looking at it from the generic side for BCS class 1 drugs, if the sponsor opts to go for an in vivo route, there is still a need to do fasted and fed BE studies, which I think should be looked into, at least for the BCS class 1 molecules and even for second BCS class 2 molecules.

Here's the typical food effect prediction or fed BE prediction that we would pursue within our organization. This is a BCS class 2 molecule. Typically, you would start with building the model. There's the single ascending dose data. Build a molecule based on that. Verify it based on previous fed fasted study. Then, again, based on the intrasubject CVs, we should be able to predict, again, based on how well the model is built, the fed BE study, and then predict that.

I'm just showing one cross-industry case study, very recent, published in 2019 from four different pharma industries, talking about the same constraints that I just discussed maybe with a little bit of a twist.

I'm quickly running out of time. I guess the case that I'm making here is the PBPK model has advanced enough where if we are able to understand the mechanism of food effect, we should be able to predict it within the constraints that are discussed here.

So, the regulatory research, from my perspective, should focus on waiver of food effect and fed BE studies. I think we can all agree that fasted study is the most sensitive state to study formulation differences. So to do fed BE studies in every case is overkill, and there's obviously been ethical, financial, and timeline considerations, too.

And specifically for the ANDA, in the ANDA cases, for BCS class 1 IER products, the need to do a fed BE study is overkill totally in my opinion.

Even in BCS class 2 molecules, there should be within certain constraints a possibility to waive BE studies based on the understanding of the molecule.

With that, I'll close. Thank you very much.

DR. LIONBERGER: Thank you.

(Applause.)

Our next speaker is Gregg DeRosa from Teva.

Presentation - Gregg DeRosa

DR. DeROSA: So that was an excellent segue into my presentation. Thank you.

We're really talking about trying to reduce the burden of proof and really reevaluating whether we really need fed BE studies or not, and we will go into some detail here.

As you know, the guidance’s are out there. It's pretty much a one-size-fits-all. We develop a product, and we have to do fasting and fed studies unless there's some sort of safety issue. This also is a requirement when the labeling of a drug a lot of times specifically states take on an empty

stomach.

Now, this is slowly changing as we get product-specific guidance's, but there are certain examples where we have to do fed studies when the label says otherwise. Obviously, that puts some burden on industry. We spend a lot of money, and we believe there's some relief that's possible.

Obviously, there's enormous amounts of things that affect the fed study result or a comparison under fed conditions and these are just a few. And we are not saying that we don't want to do fed studies at all. I mean, clearly, I think there is a need for fed studies for modified-release products that are labeled to be taken under the condition. But we really believe that there's a lot more of a simplistic approach that could be done for immediate-release products.

Just a quick overview of some of the major markets. Obviously, this isn't exhaustive, but it gives you an idea where the major authorities stand, and I think it's in stark contrast right now to what FDA is at least demanding.

Obviously, in the E.U., it's a bit more flexible, and fed studies are generally not needed other than if the labeling states so. Similar cases in Canada and Australia. It seems that the U.S. is a bit of an outlier here.

What we did, between Mylan, Apotex, and Teva, we tried to take a representative sample of fed studies and -- actually, it's programs. It's programs of products, where we had fasting and fed studies for immediate-release products. We looked at these, and we categorized them. We said where fasting and fed passed, where fast passed and fed failed, whether fast failed, fed passed, vice versa, all that.

Then, we came to the conclusion -- this included pilot studies; this included pivotal studies; and it's not a completely exhaustive end, but it's pretty large. We came to a rather simple conclusion that the fasting studies are probably the most predictive, and we'll go into a little more detail here.

We collapsed the categories into what we

believe were outcomes that were the two meaningful categories. Fasting predictive were more discriminatory than fed, obviously when fast and fed passed, when fast and fed failed, and then when fast failed and fed passed. Then when both studies failed, we thought that perhaps the fed was more predictive.

We felt, in those cases to the left, that the fed study was not very informative, and obviously, to the right, that it was. So we're looking at 97 percent of the time that we felt that the fasting study was the most informative study.

Some trends that we observed from all this data; we tried to parse it into different class compounds. Again, I don't have a breakdown of the N of each, but all of these things that we did here really are already present in literature. This is just looking at our data and saying, yes, in general trends, for BCS class 3 compounds, the food effect was negative, meaning that it was less absorbed in food studies and a vast majority of them passed at the corresponding fasting study

passed.

I think the only anomaly in all of it was the class 4's. We really felt that there were instances where fasting and food studies were different and where the fasting study outcome was certainly not predictive of food and vice versa.

Briefly, there wasn't a lot of N here, but we also looked at the idea of sprinkle studies and how they differed from fasting studies. The vast majority of these, I don't think we could even come up with an example where it didn't happen, but if the fasting study passed, the sprinkle study passed.

We're not talking specifically about crushing or disintegrating. We're talking about when you open up a dosage form and you put it on applesauce and soft food. So really, again, the fasting study was the predictive study, and this study was just add-on. And again, other regions were not requiring this type of study, and they really only rely on in vitro data.

Some brief summaries and suggestions; we

think that the fasting study is the most informative and that our data that we look through confirmed that. We'd really like to give FDA a bit more of our suggestions. We really think that having requirements that are similar to E.U. and other regions is probably appropriate.

We also believe that the label is absolutely paramount here, and we believe if the product is labeled to be taken only under fasting conditions, that's the only study that we should have to do.

While we focused on IR products, we also thought that from an MR product perspective, again, if the label states that it should be taken under fasting conditions or fed, whichever, that it should dictate our requirements.

I think the last couple bullets are summing up, again, that if the fed studies really are needed -- and I think they probably are needed in IR situations -- they should be limited to probably lower solubility products, those the efficacy is something that would be in question.

We also believe that the sprinkle studies should be waived, based on our assurance of in-vitro products that are stable on the food, and if the fasting study passes, we believe that these studies can be waived as well.

Lastly, I'd like to thank Beth, Andy, and Julie. They really put a lot of this information together, and I really thank them for their time. Thanks.

(Applause.)

DR. LIONBERGER: Thank you. Our next speaker is Zhanglin Ni from FDA.

Presentation - Zhanglin Ni

DR. NI: Good morning. Thanks for the opportunity. Today, I'm going to spend about 10 minutes discussing the scientific gaps that impact the prediction fed BE studies.

Current fed BE study recommendations; for the IR product, FDA generally recommends a fed BE study when recommending a fasting BE study, except when the RLD labeling states the product should be taken on the empty stomach or when serious adverse

events are anticipated under fed conditions.

Only a fed study is recommended when serious adverse events are anticipated under fasting conditions. For all the MR products, FDA recommends a fed BE study in addition to a fasting BE study irrespective of those instructions in the RLD labeling. The exception is when a fed or fasted study is not recommended and when serious adverse events are anticipated under fed or fasting conditions, respectively.

What modeling simulation can a fed study support? It can help identify critical product quality attributes. It can help explore the potential failure modes during the generic drug development and improve success rates of generic drugs; development dissolution and drug product quality specifications for the risk assessment for post-approval changes, and support not conducting fed BE studies.

We all know food could affect the bioavailability of a drug by various other means such as changing the GI motility and transit time,

changing the bile salt concentration, changing the GI pH and the buffer capacity, the GI liquid volume of distribution, blood flow, and pre-systemic and metabolism transport. We know food can have a direct interaction with API and/or excipients, and meals with different fat or calorie content can have a different size of food effect, and there could be other factors.

Virtual BE simulation for the fed studies that we're talking about here is based on the mechanistic modeling approaches. The goal is to predict food effect on PK for both test and reference product, namely fed B simulation based on fast and PK data.

First, a virtual population for the BE simulation should account for both intrasubject and intersubject variability in the GI physiology. We knew there's still a potential scientific gap in precise understanding of food-induced changes in GI physiology as well as a measure of the population variability.

Second, the model must incorporate

formulation variables that can represent the difference between test and reference products for perhaps fed B simulation. We know there's a gap in obtaining the biopredictive in vitro testing results as modeling input, as well as understanding the impact of excipient differences on the side of food effect. In the next few slides, I will elaborate a little more on those gaps.

Here's a GDUFA-funded research trying to look at the food-induced change in GI physiology and its possible link with intraluminal and systemic behavior of a drug product, which is ibuprofen IR tablets.

The figure on your left side is the fasting state duodenum and right side is fed state duodenum. Here, I just use duodenum as an example. First, take a look at the pH. As you can see, there's a large intrasubject variability in the GI pH. At the same time, you can see the pH changes as function of time, and at fed condition, you can see the pH decrease as a function of time.

Then we can take a look at the solution

concentration and the total concentration of ibuprofen in duodenum as a function of time. You clearly see the difference between the fasting effects stated. You also can see under fast condition large and dissolved solid ibuprofen at even a 7-hour aspiration, as reflected by the difference between the total concentration of ibuprofen and the solution concentration of ibuprofen in duodenum, which is consistent with the decreased/increase in the pH and the fatal condition as a function of time.

Research is still needed to look into more drug products such as different BCS classes, the different dosage forms, and the release mechanism. The mechanistic model should ideally not only to be able to describe systemic behavior of different drug products, but their intraluminal behaviors.

I mention this here. The post-dose phase 3 contraction and the plasma Tmax, we also see the cleared delay on onset of this GI motility and the PK metrics, and the fed condition. All those data shows a difference between the fed and the fasting

condition.

As I just mentioned, the model must incorporate the formulation variable to represent the difference between the test and reference product for the fed BE simulation. Those formulation variables should include, but are not limited to drug substance attributes, the formulation attributes, and processing parameters. At the same time, we can use biopredictive in vitro testing results as a model input for the fed BE simulation.

I'd also like to put some emphasis on the excipient effect of drug absorption because the current PBPK models do not fully characterize excipients' effects on the drug absorption. As we knew, some excipients can impact the GI transit time, and it could potentially change the GI motility. Excipients may change the formulation to the food exposure.

We knew the drug and excipient interaction occurs through the physical and the chemical interactions. In the next slide, I will give you

one example, showing you the complex effect of excipients in the in-vitro study.

The food excipient interaction may affect the rate of absorption of IR products. Therefore, absorption modeling means further research to characterize the potential in vivo excipient effects with and without food.

This study I just mentioned, as we can see, which is also the GDUFA-funded research, is the table on your left side. You see simulated gastric fluid, simulated intestinal fluid for fasting condition, and simulated intestinal fluid for fed conditions that have a different impact on crystalline solubility and amorphous solubility.

The table on your right side, I'm not going through all the details for the interest of time, but just to give you examples, the excipients such as xanthan gum and titanium dioxide have no effect on amorphous solubility or crystallization time. HPMCAS, commonly used polymer upon amorphous dispersion has no impact on amorphous solubility, but increases the crystallization time. The FaSSIF

media increases amorphous solubility, but decreases the crystallization time compared to PBS buffer.

This study indicates that excipients may have the complex effect on solubility and crystallization of API with low solubility without food in vivo.

Published in the literature review on the food effect simulation done by our colleagues that looked at 48 food effect simulation cases. What they observed was about 50 percent of total cases were presented within 125-fold, 75 within twofold, and the dissolution rate and precipitation time were the most commonly adjusted parameters where a model cannot capture well the food effect.

We found it difficult to generalize the PBPK predictability with respect to BCS class because of the limited number of BCS class 1 and 2 and 3 compounds, but they didn't observe similar predictability of PBPK model for BCS class 2 and 4 drugs.

The limitations in fed physiology implemented in current platforms, as we discussed

earlier, and there's a lag of BE simulations. It's always important to consider the publication bias when we're interpreting this type of data.

So summary, the fed BE simulation can aid generic drug development and the review, and their success for implementations can support both product development and the regulatory decision making. Both challenges and opportunities still exist in understanding the food-induced changes in GI physiology, the link between food-induced changes in GI physiology, and the intraluminal and systemic behavior of different drug products, the link between the intrasubject variability in the GI physiology, and the intrasubject variability in the in vivo PK metrics.

Both challenges and opportunities still exist in understanding the formulation variables that change food effect, and identifying those formulation variables and/or pertaining the biopredictive in vitro testing results for the fed BE simulation for the successful implementation in the future. So thanks for your attention.

(Applause.)

Panel Discussion

DR. LIONBERGER: Now we will move to our panel discussion time. The panelists introduced themselves earlier. We'll begin with any clarifying questions for the speakers from the members of the panel.

DR. VAITHIYALINGAM: Rob, I have a question for the last speaker, Zhanglin. Looking at your slide deck, I think it is slide 9 where you have conducted studies of complex excipients on API with the low solubility. Please make sure that I am reading it right. It's a low solubility, so that means it is BCS 2 or 4 molecules. Right?

DR. NI: Actually, in this GDUFA-funded research, actually, in this study, we only look at 1 API, which is posaconazole. Currently, we cannot expand to other things at this point. This one is, yes, API with low solubility.

DR. VAITHIYALINGAM: Thanks. I wish it was on a BCS 3 or something like that. Thank you.

DR. LIONBERGER: Seeing no clarifying

questions for the speakers -- I'm sorry. Ethan?

DR. STIER: Yes, one question. I just have one question for Dr. Riedmaier. I thought it was a very interesting presentation. If I understood it correctly, your group is using modeling to evaluate predicting the food effect for a compound that's in development. I'm just curious if you had any experience in terms of using those same techniques in terms of evaluating the similarity of two formulations.

There's kind of one level, trying to understand from the drug compound, for that particular formulation to say, yeah, we'll expect a higher AUC or a lower AUC, Cmax, et cetera. But in terms of comparing different formulations, where there's a significant change maybe in the second formulation relative to first formulation. Is that a clearer question?

DR. RIEDMAIER: Yes. I think so. So yes, we definitely used -- like I mentioned in that one slide where we have a verified food effect model. Once we have verified at a given dose, then we have

then applied it to different formulations.

The one challenge there is it does have to be in the same conditions as the verified model, so in some cases, if we are going with a different dose, then we'd have to do another study just to make sure that our model is applicable to that dose in cases where there's dose nonlinearity.

But we certainly have done that, to look at the effect of different formulations. That's actually a really good application of some of these models that we've developed.

DR. LIONBERGER: Yes, Jim?

DR. POLLI: I have a question for Dr. DeRosa about your summary slide; well, one comment. You indicate products labeled to be taken with or without meals should study the most predictive conditioning, fasting.

Could you elaborate more about that?

DR. DeROSA: Which slide are you talking about?

DR. POLLI: Yes. It's the summary or suggestion slide, sort of in the middle, products

labeled to be taken with or without meals should study the most predictive condition, fasting.

Can you just elaborate more about that?

DR. DeROSA: I think we've come to the conclusion, from the data that we've looked at, that the most predictive study is the fasting study, and that in an IR situation, the fasting study is the one that is the most predictive of formulation performance.

DR. SHAW: Just to build upon what Gregg was saying, looking at all the data that we collectively assess between Mylan, Teva, and Apotex, there was very few cases where we passed the fasting and failed the fed.

In those instances, it was narrowed down to class 4 compounds, but looking back, looking at all the class 1, 2, 3's, in almost every single case, the fasting predicted the outcome, whether it was going to be both failed, both were successful, or we would easily pass the fed studies, but we were unsuccessful in the fasting.

So again, it comes down to fasting as being

the most discriminating methodology that we could find when looking at 90-some, 95 percent of all the products that we were evaluating.

DR. LIONBERGER: Let me ask a follow-up on that. I think that -- let me hypothesize -- you're very good at formulating products that meet FDA's bioequivalence requirements. So during your development of those 400 products, you were intending to develop products that had similar food effects to the RLD, of course. So you are successful at that.

So here, I think we want to say what did you do and what did your formulators do? What excipients did they avoid? What choices did they make in order to ensure that those products that you did develop would actually have similar food effects?

The outcome of your development process was good, but the question is, what is the -- for the future state, when you say we have a wide variety of people who will submit formulations to the FDA, and what if they didn't do a good job of that?

What are the things that your formulation scientists had to do to do that? Did you avoid certain excipients that you, from experience, knew would cause problems with food effects, or did you say, well, this type of drug, we don't have to do that?

That's, I think, what we want to dig into; is there some kind of knowledge that the community has of the pharmaceutical science that helps us understand that? Then you would say, can we put that into our modeling and simulation or our knowledge management framework that helps make those predictions in the future?

I think the perspective you're hearing from the FDA is we have to guard against any random formulation that someone anywhere in the world develops the potential generic and sends to us, and says, "Can I market this in the U.S.?"

We don't necessarily know that they, in their pharmaceutical development, have made the right choices to minimize that food effect. I'm interested in your perspective on that comment.

DR. DeROSA: I think putting boundaries around these things is the right thing to do. I think the idea of every formulator is to match the product that they are looking at. How to guard against what you just talked about? Yes, there's going to have to be a whole lot more research.

I'm certain that there is a lot of data that we could glean from our databases, and yours, that could help us get there; absolutely.

DR. LIONBERGER: Bing?

DR. LI: Yes. My question is actually along with Rob's comments. For that 5 percent of cases where the fasting study passed and the fasting study failed, are there any considerations to exclude the formulation factor as well as the inactive ingredients factors to conclude that 5 percent failing is contributed by the insoluble or poor solubility of the active compound?

DR. DeROSA: Yes. I think we'd have to do a bit more research on that. We had a finite time, and we tried to glean as much information from the databases as we could. When we sat down together

and just tried to come up with, here's the data that is presented to us, it was glaringly obvious to us, at least from our data, that there was a trend here, that fasting studies were predictive.

Why those certain subsets failed? The only thing that we could say from the limited amount of time and data that we had was these are pretty much poorly soluble drugs. We didn't look at formulation differences. There was not enough time to do that, but it's certainly something that we could go back and look at. I think it would be very valuable.

DR. LI: Yes. As the Office of Generic Drugs, we think of this issue from the generic [inaudible - mic fade] -- comparing two products, same API, same relative administration, same concentration, same dosage forms in where the differences lie in the inactive ingredients and the way they're formulated.

That factor is critical for us to be able to adopt a way that the formulation and the inactive ingredients -- how to translate whatever

you found in the new drug to generic drugs arena.

DR. DeROSA: I understand, yes.

DR. LIONBERGER: Sid?

DR. BHOOPATHY: This is a follow-up question for Dr. DeRosa. Just going back to what Rob had just mentioned, your formulators are setting it up to pass the fasted and the fed study. Before performing your pivotal fed, you want assurance that this is in the right direction.

Do you do that through some type of in vitro test, or is it a pilot-fed study, or is it some modeling being brought in with maybe some in vitro parameters? How do you increase your probability along the way?

DR. DeROSA: Typically, it's a lot of in vitro work through dissolution, obviously particle size, all sorts of formulation techniques to really show that you're the same. Then we usually do pilot studies, and we go from there.

You have to understand -- I think Andy will probably agree with me -- that the modeling piece only happens after you've been unsuccessful for a

few times. Honestly, we always believe that we're going to be successful based on the in vitro parameters, and then we move forward into pilots.

So modeling in and of itself in the very beginning from a generic perspective, for an IR product, probably would be not as prevalent.

DR. SHAW: So just to build upon what, Gregg, you said, I 100 percent agree with you, how we look at it, in terms of, yes, we're going to look at doing a potential pilot study. But a lot of times for an IR product, after we do all the in vitro characterization work, we're going right to pivotals because we have a high probability of success, within IR, that is.

Dr. Lionberger, getting to one of your questions, when we initially go after a formulation, we already know, obviously, what's in the reference from a qualitative perspective, and we know what, typically, in our plants and our manufacturing processes, works. We're not going to try, for an IR product, to come up with the unique or novel excipient that we're going to put into it.

We're going to start off with stuff that we're used to working with, so you're looking at GRAS type products.

DR. LIONBERGER: Yes. I think the challenge for it, if you want to evolve the regulatory landscape, is how do we capture that in a way that helps our reviewers make a decision to say that this formulation that someone has submitted to us is within that scope of these are excipients that aren't going to have that effect without doing the sort of just do the study and then we'll know for sure.

I think that's what we're trying to capture, formulating the scientific question. How do we establish that knowledge in a way that's useful and actionable for FDA's review staff to say, "Oh, I also agree that this formulation is using a set of excipients that, based on our understanding, is not going to cause a different food effect."

That's what we're trying to get at, is can we quantify or establish that knowledge information

in a way that our reviewers can use.

DR. MITRA: It's totality of the data. That's what we should be looking at. If I put a counter-argument to that, just because you're doing fed studies in "healthy volunteers," quote/unquote, how does it translate to a subpopulation with a chloralhydrate or something like that?

There would be no end to that argument. So it's a totality of the data, and I think modeling and simulation plays a huge role in that. At least from our perspective, in our organization, we use modeling routinely before any PK study. Even after pilot studies, before a pivotal study, we do use modeling to study formulation changes and such.

So I think, at least from our perspective, what you are asking for is flexibility in the guidance's, not just limited to do fast and fed BE studies, but there is some flexibility that, anything else, in vitro characterization, modeling and simulation, whatever that may be, is put into writing, so the sponsors have the opportunity to explore them and not be stuck with the fed-fasted

study.

DR. LIONBERGER: Is there any in-vitro -- for the immediate-release different BCS classes, is there an in vitro experiment, a dissolution experiment, that from the industry's perspective, you find valuable to say this is something that's going to tell us whether there's a higher risk or a lower risk of a food effect? Has that been established?

Also, Jim, maybe you can comment on this, too, in terms of the different proposed simulated media for dissolution that has been proved reliable to say, I'll do this dissolution test under this condition, and that will tell me there may be a problem here.

DR. SHAW: Just to clarify, you're talking about across the board, not product specific.

DR. LIONBERGER: I mean, if you just say, well, for some products, this is work. I want to understand what the state of the knowledge is about of using a dissolution method with, say, more in vivo relevant media to say, I'm going to get

information that's useful at predicting that there might be a formulation-dependent food effect, or a food effect in general. If you don't use it, if it's not something that you --

DR. SHAW: From at least my perspective, we haven't found one that's universal. We might have found one that we might have had a correlation, but we've noticed it's been more product specific.

DR. MITRA: I would agree with that. I think we need to be careful on biorelevant versus biopredictive. Just because it's biorelevant doesn't mean it's predictive, at least from my experience.

Again, I will tie it back to all the biopharmaceutics tools we have. I don't think we need to necessarily have a universal dissolution media for all BCS tools, or BCS 1's, or whatever the BCS class be. You need to have a method for a product and show it to be biopredictive for that product. And again, it comes to the totality of the data, I think, and not just universal method.

DR. LIONBERGER: First, and then MJ.

DR. FREDO-KUMBARADZI: In terms of dissolution, we all know that it can predict the solubility, but not the absorption part. It can be predictive for the cases where the solubility is the rate-limiting step, but when absorption is, then we are not simulating the disappearance from the absorption site, and obviously, information from biorelevant media would be very limited.

Nevertheless, I don't think that there is one solution for all, but as mentioned several times, there are products of different complexity where excipients are simpler, or compositions are complex, and processes are complex, so food effect may be different potentially.

But we have to be aware that, for a simple formulation of immediate release, in fed stomach, excipients are disengaged from the active, with the food being in such an abundant amount, impact of excipients is less likely to be there, more likely under fasting condition when there is nothing else but excipients and gastric fluid, the drug substance. Therefore, we have to look from

complexity point of view and think about those, simple and complex cases, separately.

DR. LIONBERGER: MJ?

DR. KIM: This is somewhat deviating from the formulation or excipient related in terms of the food effect. I'm going to try and take my regulatory hat off and pose questions to the industry in regards to the food effect in drug development.

My question is, when you assess how to do, or you want to do, or if a BE study under fed condition is needed, if you are to go back to the reference-listed drug product labels, oftentimes, the instruction may be somewhat ambiguous. It's not just clear fed and fasted. Also, it depends on how the phase 3 studies were conducted, regardless of the dedicated food effect results.

My question to industry is, when you contemplate about this food effect and the fed BE studies, how do you deal with what was already done with the reference-listed drug and what the limited or sometimes unclear instruction under the label

may be saying with regards to the food intake, or how to, or when to take it, such as taking the drug at bedtime and what the findings from the phase 3 studies are in terms of the food?

Can you elaborate a little more on this, stepping beyond the formulation or nitty-gritty scientific aspects, and look at it from the clinical implications? Anybody?

DR. MITRA: If I could clarify that a little, are you talking about, for example, circadian rhythms or like a low-fat meal, and things like that? Are you thinking about that?

DR. KIM: Right. The food effect is not so simple. First of all, the labeling can be sometimes not clear. Sometimes, it does say take it maybe 1 hour before or 30 minutes, and sometimes the RLD drug label says, "Take the drug at bedtime," maybe with food and things like that. But then for the bioequivalency, one may need to do the study in healthy volunteers at daytime.

I'm posing all these questions, stepping above the typical formulation.

DR. VAITHIYALINGAM: During the initial phase of development, all these things are taken into account. For example, if you look at the esomeprazole, it says it has to be taken an hour before a meal. That means there is a certain hindrance for the absorption of solubility or for the mechanism of action for the drug that has clearly been captured. We do a lot of due diligence on why that statement exists, and then go back to the development and make sure that is captured.

Secondly, if you take some drugs where you have to take before sleep, that means it affects the circadian rhythm. That means it has a biphasic or monophasic. Those kind of things are taken into account for how to formulate.

So yes, it is true we study the RLD package insert as much as possible, and also a certain level of phase 3 clinical trials and how the review is done, and what are the review findings based on freedom of information. We take that into account during the designing and development.

This is just all I'll answer, but if you want, we can go specific offline. Thanks.

DR. LIONBERGER: So we're closing down, so please prepare your final comment. I'll do one last question I'd like some comment on, especially for the generic drug developers.

Does the magnitude of the food effect that you see for the RLD affect your formulation and your decisions about the development of the generic product? If you see the RLD has a big food effect, what does that do to your formulation development and decision processes?

DR. DeROSA: I don't think it does anything. When we are looking at developing a product, again, to Siva's point, we know what the characteristics of the product and the drug substance are from a generic perspective, and it wouldn't dissuade us or change probably our development techniques if the food effect was large.

DR. SHAW: I concur with Gregg. From our aspects, we know FDA's expectations are fast and

fed. We're developing the same formulation worldwide or attempting to do the same formulation worldwide. If we know we're going into the U.S., we know we've got to do a food study, so we just chalk it up.

DR. LIONBERGER: Are there any final comments from the panel on this topic?

(No response.)

DR. LIONBERGER: Thank you, all. We'll be going into our 15-minute break. We will reconvene at 11:00. Remember, the most important thing you need to do during the break is order lunch if you would like lunch. Thank you all very much. We'll be back at 11:00.

(Whereupon, at 10:44 a.m., a recess was taken.)

Public Comment Period

DR. LIONBERGER: Welcome back, everyone. For this next session, we'll have two distinct parts. We'll have our open public comment period, so we'll have two speakers who signed up for the public comment period first, and then we'll have

two presentations related to the implementation of novel methods that have come out of our regulatory science program.

To begin with, our first speaker in the open public comment period is Jurgen Bulitta. He's a professor at the University of Florida.

Presentation - Jurgen Bulitta

DR. BULITTA: Thank you, Dr. Lionberger, for this kind introduction. It is my great pleasure, and I thank the organizers for the invitation to present this research conducted by Dr. Hochhaus in my group in collaboration with a great many collaborators.

We want to perform research to establish the central role of pharmacokinetic studies for a streamlined development and approval of generic inhaled drugs. There is, of course, a great need of inhaled generic drugs, and this creates pressure for a streamlined development in the approval process. The FDA has been mutually active in this area over quite many years. Dr. Hochhaus has been part of this for, to my knowledge, already 10

years, and I've been very fortunate to join his group and team over the last three years.

We were, in this study, primarily interested in slowly dissolving drugs, either negligible [indiscernible] or bioavailability, so F oral is 0. For both types of drugs, we hypothesized that pharmacokinetic studies can provide important information, which is necessary to assess pulmonary bioequivalence.

The three metrics we use to evaluate pulmonary bioequivalence are the available dose to the lung, measured by the area under the curve in plasma; the pulmonary residence time, characterized by the P concentration and its timing; and then finally the regional lung deposition, central to peripheral ratio.

The hypothesis above would predict for a formulation which deposits more centrally, but such a formulation would have a lower area under the curve. The idea here is that if more drug is deposited centrally, the mucociliary clearance, so the removal of large particles from central

portions of the lung, has a larger impact for such a centrally depositing formulation, and therefore, the AUC is lower compared to a more peripherally depositing formulation. Likewise, a more centrally depositing formulation is expected to have a lower Cmax because there is just fewer drug available for the rapidly absorption part from the peripheral lung.

A human clinical trial, a four-way crossover, was performed in healthy volunteers. Formulations were designed by our collaborators at the University of Bath, Rob Price and Jag Shur. They engineered formulations, which had different MMADs, but they used to same API. Formulation A had the largest MMAD, and then formulation B and C and C repeat had a considerably smaller MMAD.

Mike Hindle's team at VCU performed in vitro studies to assess the total lung dose by in vitro methods, and in Dr. Hochhaus' lab, dissolution tests were performed to assess the rate of dissolution of flucticasone propionate DPI formulations.

We found that pharmacokinetics could inform and provide critical information for the total lung dose, so the AUC, also for the pulmonary residence time, characterized by the peak concentration with or without normalization by the total dose. And we found that it was central to peripheral deposition ratio and was perhaps best informed by Cmax over dose.

This was a relatively clear outcome, as I will show in later slides. The area under the curve was not as directly informative as Cmax over dose. This gives rise to ongoing research, but we certainly feel that this was a very valuable study for gaining further insights into pulmonary bioequivalence.

Outside of the main conflict for the study, we performed a population PK analysis, which gave us further granularity for the processes involved in pulmonary absorption. The lung was separated here in the central and peripheral portions, and we could estimate the bioavailabilities for both central lung, FC, and the bioavailability for

peripheral lung, FP, as well as the associated absorption half-lives from each of the portions of the lung.

The model worked very well and was also quite robust. The key parameters related to pulmonary absorption are shown on this slide. The first two lines show the absorption half-lives from central and peripheral lung for the three formulations, so A having the largest MMAD, and B and C being very similar with an MMAD of 3.7 and 3.8.

As expected, the absorption half-life from peripheral lung was at least 10-fold faster than the absorption half-life from central lung for all of the formulations. When both were central and peripheral lung, formulation A had a slower absorption half-life compared to the smaller formulations, B and C.

Now, when it came for the absorbed dose from central and peripheral lung, we obtained very exciting results. The bioavailability from central lung was almost identical between the three

formulations, around 6.1 to 5.3 percent. However, formulation A clearly distinguished itself with a much lower bioavailability from central lung with only 1.7 percent, compared to about 6 percent for the other formulations.

The central to peripheral lung deposition ratio was clearly different based on this population PK modeling analysis for the large formulation A compared to B and C, with ratios of 3.1 for A and around 1.0 for B and C.

In summary, pharmacokinetics in population modeling could clearly provide important information on the regional lung deposition of this already inhaled DPI formulation. However, population modeling, as much as many of us, including myself, love it, is an involved technique, and there is more wiggle room for doing certain assumptions during modeling as opposed to standard non-compartmental PK methods.

Therefore, we propose future research to evaluate simpler approaches based on non-compartmental analysis to inform regional

deposition of the lung for inhaled drugs, but to support these types of non-compartmental analyses by insights available from population PK and physiologically-based PK modeling.

This is a simulation, which shows the impact of different absorption half-lives on the p concentration to be expected. Here, formulation A clearly had a slower dissolution time of 19 hours compared to 13 hours for formulation C.

This was inserted into a physiologically-based pharmacokinetic model using the Nernst-Brunner and the Fick's Law equations.

Dr. Hochhaus' team predicted if two formulations have the same central to peripheral lung deposition ratio, even a much faster dissolving formulation, C, would only achieve approximately a 15 percent higher peak concentration.

What we observed for in the clinical trial was that the peak concentration for formulation C was 80 percent higher than that of formulation A, clearly suggesting that there is sensitivity of Cmax to inform about the central to peripheral lung

deposition ratio.

In summary, non-compartmental pharmacokinetic analysis, based on a human clinical trial, could provide information on the lung dose, the pulmonary residence time, and also the regional lung deposition. At the moment, we believe it is good sensitivity for Cmax, or for a dose-adjusted Cmax, or Cmax divided by dose.

For future research, we believe it is important to assess the robustness of these non-compartmental approaches to assess pulmonary bioequivalence, and this would be proposed to be performed using population PK and physiologically-based pharmacokinetic modeling. We would like to generalize this approach to other drug classes such as other corticosteroids, long-acting beta agonists, or antimuscarinic agents.

The overview of this flow chart is on this slide. We start with compartmental modeling at the top left, so this is population PK, and when simulate, virtual bioequivalent studies by systematically providing the regional lung

deposition, the total lung doses, and the absorption half-lives.

The bottom part shows a more mechanistic approach, leveraging physiologically-based PK modeling, which involves an array of in vitro assessments to inform these models and implementation of physical-chemical drug properties. We would need to add between subject variability and within-subject variability to the PBPK model in order to simulate virtual bioequivalence trials.

These two more empirical and more mechanistic simulation approaches give us the ability to assess the robustness for the sensitivity of pharmacokinetic studies to assess bioequivalence of RLD orally inhaled drugs over a range of drug classes.

A second area where we believe some research would be of interest is a systematic evaluation of the ex-throat plume properties for metered-dose inhaler formulations. We are proposing to consider a variety of MDIs and combine

them with different available mouth, throat models, 8 of those, and things like droplet size distribution, APSDs, the plume geometry and dissolution profiles would be recorded in an effort to better understand what are the most realistic and most informative testing conditions for these metered-dose inhaler formulations to make decisions for regulatory development and approval.

Thank you very much for your attention, and I really would like to greatly acknowledge that this is work from many people who very nicely work together.

(Applause.)

DR. LIONBERGER: Thank you very much.

Please take a seat in the audience, and if the panel has any questions during the discussion, we'll call you back up.

Our next public comment speaker is Priscilla Zawislak. She represents IPEC Americas.

Presentation - Priscilla Zawislak

MS. ZAWISLAK: Thank you. Good morning, and thank you also for the opportunity to speak

today. I'm representing the International Pharmaceutical Excipients Council of the Americas, and I'd like to talk about assessing excipient solutions for generic drug development.

As you all know, excipients play a very important role in the quality and development of generic drugs. New excipients, however, are also needed to provide functionality, as well as performance, for emerging therapies to lower the cost of pharmaceutical products and also to meet processing needs; for example, continuous manufacturing. FDA needs to be able to evaluate new excipients developed to meet these demands.

To improve generic drug development and make things more efficient, it's essential that a process exists to more easily evaluate the safety of all excipients, including new excipients. So IPEC has two proposals that we'd like to present today, which we believe are essential to facilitating FDA's evaluation of these new excipients.

Our first proposal is for FDA to evaluate

how the Tox21 concepts can be integrated into future safety evaluation requirements for novel excipients. We believe the FDA should sponsor research projects to develop Tox21 concepts to use in lieu of current animal study requirements and also update this current guidance to incorporate the Tox21 concepts, and the guidance is here, the one for the nonclinical studies for safety evaluation of excipients.

The outcome that we would expect from this initiative would be to have CDER aligned with FDA's predictive toxicology road map for integrating novel predictive toxicology methods and to safety and risk assessments of its products. We also would like to see reduced animal testing, which is a part of that program.

Our second proposal is to sponsor research to establish the safety study requirements designed to cover different grades of the same excipient or what we call excipient families with similar toxicology and safety profiles to support the bridging justifications that the generic companies

must do to submit their ANDAs today.

We believe that the FDA should sponsor research projects to study toxicological effects over a range of excipient polymers, and we would suggest perhaps starting with maybe two of these excipients that are very common that may differ only by molecular weight or viscosity. Also, we would like FDA to update the excipient safety guidance mentioned here to reflect the appropriate studies for similar excipient families that could support the bridging approach.

The outcome that we would expect for this would also be tox studies defined, which could cover entire families of excipients that differ only by certain properties and also alignment with FDA's Tox21 initiative and reduced animal testing.

One example I'd like to give for proposal number 2 would be using hypromellose, which is obviously a very common excipient used in thousands of drugs. The boxes that you see in green are the established types that are in the USP monographs and in other pharmacopeia. There is another series

of HPMC HME for hot-melt extrusion, which is the P series, and this is a modified HPMC, but it is still HPMC in all respects, the same toxicology and safety profile as all the other types.

Using this concept, we have already done a lot of studies that are in the blue circle, with the toxicology of a range of HPMCs, and all of the data has come out the same. But if you look at what's in the inactive ingredient database, we're really talking about the maximum potency levels only being a few milligrams up to maybe a couple hundred milligrams, whereas, if you look at the red box on this, which represents the entire monograph that is in the USP, this is also something that FDA CFSAN has approved everything within this range of HPMC substitutions at a daily intake of 20 grams per day. We're not talking milligrams here. We're talking grams.

So we'd really like to see the application of these Tox21 concepts to supporting, perhaps, these studies that have already been done and try to bridge some of these newer grades to demonstrate

the feasibility for the safety and toxicology of these grades.

One of the other benefits that could come as a result of this would be an improvement to ensure that the Global Substance Registration System's nomenclature, chemistry, and accuracy for that, and also the integrity of the information in there because we do know that there's still quite a number of issues with that, and it would certainly open the use of some of the existing excipients as well as some modifications of those to faster approvals and to gain more acceptance by generic companies to use these in formulations.

IPEC will also be submitting more detailed comments to the docket. Thank you.

(Applause.)

DR. LIONBERGER: Thank you very much. Again, please sit down, and then the panel will be asking questions.

Our next speaker is Darby Kozak, who's a team leader in the Division of Therapeutic performance in ORS. He'll talk about some of the

challenges in implementing new analytical methods.

Presentation - Darby Kozak

DR. KOZAK: Thanks, Rob.

As he said, in about the next 10 minutes, I'd like to highlight some of the new analytical methods that have come from or been investigated as part of the regulatory research of science initiatives for the last few years, and specifically to get more public feedback, as well as industry's feedback, on the perceived advantages and challenges with these methods and what new research needs to be done in this sort of space.

Over the next 10 minutes, I would like to highlight three key components. As I mentioned, one aspect here is some of the past research science initiatives that have been identified with new analytical methods, specifically the characterization methods for complex active and inactive ingredients, as well as characterization of complex particulate systems, or colloidal suspensions, or particle analysis methods.

I'd like to present a couple of examples,

like I said, highlight examples of what are these new methods and what we see as the advantage of using these methods, specifically some of the characterization using NMR of complex polymer structures, some NDRS, as well as Raman spectroscopy for the particulate systems, and then some of the new capillary electrophoresis and isotope used for a free versus encapsulated drug.

Lastly, the most important; I want to encourage as well as open the conversation a bit more about the routes to engage FDA, especially OGD through the GDUFA research plan, on how to implement as well as to present some of these new analytical methods.

As I mentioned, over the last few years, we've had a series of research initiatives. Last year, 15 were identified and two of those were specific to the analytical methods. A1 that was published out, was to improve the advanced characterization for chemical compositions of molecular structures of complex API. The other is new methods to improve particle size, shape, and

surface characterization.

On the first realm, what we can see is potentially why this is an important thing to understand, the characterization of complex active and inactive ingredients is, specifically, a generic drug product needs to contain identical amounts of the identical active ingredient as a reference-listed drug to become a generic.

There are actually inherent challenge, especially with the complex actives, so new analytical methods may be able to address being able to assess and characterize and establish sameness or demonstrate sameness of complex active or inactive.

Specific ideas that we looked at in terms of complexes is heterogenous mixtures of active moieties, where you have a series of mixture of active moieties that you need to identify the overall structure, as well as the mixture of those. Those can be such things like conjugated estrogens or glatiramer acetate.

Another complex active is actually the

heterogeneous chemical structures, polymeric materials that have multiple monomers or co-polymers and blocks, and what you need to identify and show that you have some structure and sameness to show that the active is the same there. These require some new analytical methods compared to what has been done for small molecules.

I mentioned I would generally will go over a couple high-level case studies, as to where we see has been the advantages of our research in this space and how it's potentially helped industry as well as the regulatory review of these drug applications.

One case study here is the use of the carbon 13 NMR to better understand the chemical structure of this polymeric API, which is sevelamer and sevelamer carbonate, which incorporates two different monomer units and then sometimes cross-linking here.

You can use the NMR to get the understanding of the overall chemical structure, being able to then compare the different peaks

associated with the different chemical structure backbone of that polymer, and be able to compare that through.

So within the aspect of the outcomes of this, we've been able to not only publish our product-specific guidances, our articles to demonstrate the method, but there's also been approvals of these two drug products, the sevelamer carbonate tablets and 9 ANDAs so far.

Another example of the use of NMRs when in the inactive, complex inactives, is the polymeric PLGA, which is a co-block polymer. It's well known that the ratio of the different monomers, the lactide and glycolic acid, as well as overall molecular weight can have a direct effect on its release of the drug and the overall biodegradation of the drug, the formulation when injected, as well as the in group.

Some of the components there is the research done on the NMR to show that you were able to use the NMR to be able to characterize the LG ratio, as well as the ester end group there.

There are multiple products that contain these PLGAs, and the idea here is we're doing the research in this space, publishing out and demonstrates the fact that there are methods out there that can do it as well as hopefully provide examples that the industry can perform and FDA knows how to look at when they review.

In the same case, we've also looked at more complex polymer structures, where you go from a linear versus a star polymer, understanding now if you've got multiple arms to that, what type of characterization methods you could use.

In this instance here, there's been some more higher analytical techniques such as triple or quad detection, SEC/GPC, to better understand what properties can be measured and can we differentiate between a linear and star-shaped polymer. As I said, these are all important components when you're actually demonstrating or developing your generic product to show that your formulation's the same to the reference product and go through that process.

Within the second GDUFA priority here is the characterization of particle size and shape. I think we've heard already a couple talks today, as well as we have a general understanding of the performance and quality of the drug product can depend on the properties of the particles in that formulation.

Really, as we're getting in there, there are a lot of new analytical techniques being developed in this space that have higher resolution, sensitivity, and accuracy and the role that these instrumentation can play in demonstrating the sameness.

In examples down at the bottom here, you have a liposomal where you can actually look at using cyro EM or cryo SEM, the actual structure of those liposome particulates, as well as potentially within the case the doxorubicin, the precipitation of API inside the liposome.

That gives extra confidence that your formulation is similar, as well as the new methods can also look at non-spherical mixed particle

systems, as well as the overall stability, looking at crystallization formation and over the shelf life of transdermal patches.

For brevity, I'm going to give a high level, couple examples here, where new instrumentation such as the morphologically-directed Raman spectroscopy can be able to identify heterogeneous mixtures of particulates. Here's where you have a system where you've got API particulates mixed with your excipient particulates.

You really want to know now what's the overall effect, or the size distribution and characteristics of your API, so you're able to then use this imaging technique as well as the Raman chemical analysis to identify just the API particles and get the characterization of that without having the mixture of the excipient within there as a co-contaminant.

A secondary case here is looking at the overall quality of a transdermal product, where you can look at the overall shelf life using things

like polarized light as well as Raman spectroscopy to better understand that, over the duration or aging of this product, you'll begin to see crystallization of the API out.

You can then determine, over the timeline as well as the API loading, that the crystals forming are API or if they're excipients, and better understand that fundamental understanding. This kind of gives us a better understanding really to get a more appropriate shelf life as well as in the development of those drug products.

The last method I want to kind of highlight, like I said, there's a lot of new analytical methods that our research science initiatives have investigated, but like I said, this is just a high level.

The last one I want to kind of go into -- because one of the complex issues that we often face, especially with the liposomal drug products, is how much drug is free, meaning outside the formulation, and how much is contained and encapsulated, and how to accurately measure that.

There have been studies in terms of using capillary electrophoresis, which can, in vitro, look at the amount and separate out the amount of free drug versus the amount of encapsulated drug and calculate that, as well as using things like a dope-stable isotope to actually measure the free as well as the encapsulated within plasma PK samples; the idea being that if you can get a more accurate and precise measurement here, you could potentially get a lower number, or you don't need to require as many sort of patients or power that PK study to a higher degree to account for that variability within the analytical method.

So on the last component that I really want to kind of highlight a little bit more is how to engage FDA on some of the analytical methods. We do a lot of research in this space, but when an industry has a new analytical method, we have a couple different mechanisms in which to be able to engage FDA.

One is if you're already using it within your actual generic product development, come to

the FDA through -- we've got the new pre-ANDA product development meeting program as well as the pre-submission program.

In that aspect there, you can then start to engage FDA science staff on what this new analytical method does, how it can benefit the BE as well as quality perspective and its analysis, and that gives a discussion back and forth, educating both the agency as well as you, and we can have that conversation.

The other aspect here is when developing a new analytical method or proposing a new analytical method, but necessarily not with already an ANDA, as we were doing here today, what types of new research do we need? What new type of analytical methods are out there that we might not be aware of?

In that aspect here, this is the GDUFA research public workshop. It's your opportunity to engage with us now. Let us know what new analytical methods we should be looking at, which things are promising, which have advantages, and

which ones do you see potential issues with.

You also can engage, if you have a brand new analytical method or new sort of proposed technique, through a broad agency agreement or even granting opportunities, and those are all available on our research website.

I want to leave with you today, essentially, FDA is engaged within the latest science. We want to be able to do research in new analytical techniques, and we see a general benefit for both industry as well as the agency, and we encourage you to then engage with us on which research we should be doing and focusing on.

As I said, it's a lot of work from a lot of different people, and I hope that I've acknowledged everybody within this space here, but I'm sure it needs quite a few more names within that. These are just with the internal, but we also have external researchers, too, and I would like to acknowledge everyone that's been a part of the GDUFA research program.

DR. LIONBERGER: Thank you, Darby.

Our next speaker is Liang Zhao. He's the director of the Division of Quantitative Method and Modeling within OGD-ORS, and he'll talk about novel quantitative methods.

Presentation - Liang Zhao

DR. ZHAO: Thanks, Rob.

Darby just mentioned how to engage novel analytical methods to advance the regulatory program. I will be focusing on challenges for industry in implementing new computational method that arises from the regulatory science initiative. I also want to thank the previous presenters who have already highlighted a lot of new advances in the field to facilitate the generic development under review. A disclaimer; you can read it.

Today, we already know from a previous FDA workshop, we have lots of talks regarding leveraging quantitative method and modeling to modernize generic drug development under review. That includes a panel of in vitro BE methods such as the earth mover distance method; in vivo approaches, which include dose scale analyses and

Emax models, and can we further enhance the techniques and the computational approaches behind these conventional approaches?

Today, I'm going to focus on the value of using virtual BE simulations based on either a population-based PK/PD exposure-response models or mechanistic models, including PBPK approaches.

I will have two cases using PBPK approaches to the generic development and review, and one case arises from the introduction in the pre-ANDA stage with the applicant. This highlights how to use the PBPK analysis to support and alternatively be the approach for a metered aerosol product.

The background data and alternative BE approach was proposed, including the in vitro test and PK studies, but no comparative clinical endpoint study. The firm provided predictions from computational fluid dynamics on PBPK models along with data from additional in vitro testing to justify their BE approach. The question to us is, is this method viable?

I just want to download here that our

internal response opinion is that, with efficient model verification, the PBPK modeling approach can be used as a part of the evaluation as to whether the in vitro and PK studies provide evidence of locally delivery equivalence. We said yes.

The second case arose from an actual ANDA review. The applicant included a PBPK modeling package to support BE evaluation for a topical product. They also evaluated a proposed alternative approach for BE evaluation, which includes dermal PBPK as a part of not conducting, again, a clinical endpoint BE study, which could be costly and sometimes insensitive. The question is, is the proposed alternative BE approach acceptable?

Based on internal evaluation, we think the PBPK model helped us understand the systemic to local link and supports the proposed alternative pathway. The in vivo PBPK studies supported the BE assessment on a product approval without conducting a PSG recommended comparative clinical endpoint BE study. Certainly, to enable the model to make a regulatory impact is going to be a review issue,

and the model should be sufficiently verified.

Out of the practice, we do feel that new methods always come with a cost. It always comes with new challenges. Even though with publication of PBPK guidance regarding submission format on content, we still think the application can be further improved with the following list.

Appropriate documentation of the entire model development process, should it be included. If you use literature or other data sources for the modeling development, verification needs to be properly accurately cited. The rationale behind the various decisions made during model development need to be clearly stated and supported by scientific evidence.

Verification standards need to be stated at the initiation of the model verification process and applied throughout.

Incorporation of quality attributes, which is very important. In generic drugs, the main thing is to evaluate the impact of formulation, the formulation factors and impact on the clinical

performance of PK exposure. Incorporation for the quality attributes for the drug product of interest is an important component of model structure.

For locally-acting product, they do need actual layer of thinking regarding with model verification. The model needs to compare model-predictive drug concentrations in the local tissues with experimentally obtained values when available in addition to assessing model performance at a systemic exposure level, and incorporation of a compound with local in addition to systemic experimental data to the verification plan is desirable.

So the point to use a PBPK model in place of clinical endpoint study boils down to whether the PBPK model can really be a surrogate to estimate local drugs at the site of action. We need to keep that in mind in the modeling development verification and submission.

Let's take one step back. Over the years, we see -- I'm so glad today we see several modeling-focused presentations already happening in

the generic drug development and review. The challenge is to implement a new method from the generic industry in our understanding, and it comes down to lack of initiative and awareness; lack of resources, investment, and convention in generic firms.

Here, I would really want to encourage generic industry to think and use a quantitative method of modeling and evaluate the investment on return for applying them. You can be pleased by investing in this type of method in your development program, especially for complex products.

There's always an inverse relationship between method, complexity, and standardization. The more difficult the method, say, a very complicated PBPK model, it's hard for us to standardize the review process or the verification process, which can lead to difficulty in communication to industry what we are expecting and what you can do exactly to meet the regulatory need. It could be a case-by-case basis at this

point.

We do realize there is under development of the ecosystem between agency and the industry for quantitative methods and modeling. Regarding the ecosystem, we are talking about a culture, a convention, between regulatory agency and the industry, and the ecosystem should promote initiatives for method development and implementation from both ends, not only from the regulatory agency.

We need to have a timely scientific exchange. We need to have multiple sources for software implementation such as open source or commercial source. We need a guarantee there is a flow of talents across industry to the agency, from agency to industry, and within industry from generic to new drug, from new drug to generic, so we can share the latest cutting-edge technology on the initiative application.

We need those ecosystems to foster the next generation of industry experts from within. We do have an official channel to communicate through the

pre-ANDA meeting, and we can discuss general issues in workshops, conferences, and any such kind of venues.

My final question to the panel for the following panel discussion is what can FDA do to grow the ecosystem? Also, with the lists of publications, guidance, PBPK model verification, conference workshop, code sharing, what do you think? Which of these are the most critical to address?

I will conclude my presentation for this, and looking forward to further panel discussion.

(Applause.)

Panel Discussion

DR. LIONBERGER: Thank you, Liang.

Now we have a panel discussion. First, I'd like to ask any of the panelists if they have any questions for any of the speakers. This includes the public comment speakers. So they'll be available to come to the microphone if you have any questions for the speakers in the public comment period.

DR. HOCHHAUS: First off, Bing and then Guenther.

DR. LI: Yes --

DR. LIONBERGER: Who is your question for?

DR. LI: My question is for Dr. Bulitta.

DR. LIONBERGER: Can you please come up to the microphone?

DR. LI: I feel one of the hot topics that we are discussing today is to get rid of this clinical endpoint study. If we are talking about INDP, inhaled and nasal drug products, we are talking about this suite of evidence approach, in vitro, PK, clinical, and formulation similarities?

I feel that the more understanding that we have with regard to the PK study, the more tendency we are approaching to having the clinical endpoint study out of our pictures. So thank you for the valuable information that you put in.

My question to your presentation is you chose a model fluticasone as your model drug, so I want to understand what is your rationale to choose

this model drug. Furthermore, how would you translate or extrapolate the conclusion that you get from this model to other inhalation drugs?

DR. BULITTA: Yes. Well, of course, this is a very critical question. Fluticasone propionate was chosen because of its low solubility and high permeability. Whatever drug is deposited in peripheral lung is assumed to be very rapidly absorbed because permeation from membrane is more or less instantaneous. If you choose this drug class, you should get a large impact of mucociliary clearance because dissolution in central lung is not going to happen immediately.

Now, we are currently doing one other clinical trial on mometasone furoate with FDA, but data are not yet available for this one. So I believe we have to be somewhat cautious to extrapolate this one too aggressively.

At first, of course, we used simulation approaches as outlined with PBPK, but for this relatively complex space of PK and PKPD of inhaled drugs, I believe we are not yet at the stage of

doing a full globalization.

Guenther, do you wish to comment?

DR. HOCHHAUS: Yes. I agree. We used fluticasone because it was, yes, as you said, very lipophilic, and the original hypothesis, that mucociliary clearance, would give us information on central to peripheral deposition ratios, what's there. We probably could say right now that whatever we have shown for fluticasone might be applicable to similar compounds like mometasone furoate.

Within the work that we did, we learned that we also might expect really differences in absorption rates due to differences in the deposition. We're going to publish collectively soon somewhere where we can say that the absorption of fluticasone propionate from the alveolar region is relatively fast, as Jurgen has shown, and purely driven by dissolution; while in more central regions, the drug actually dissolves under non-seen [ph] conditions, and it's much, much slower. So the Cmax value will give us some additional

information on regional deposition.

If you look at compounds also from other drug classes, there are some examples for olodaterol and tiotropium, where Pop PK analysis also showed that they are biphasic or triphasic absorption processes. And you could speculate that those absorption processes also represent differences in regional deposition.

So the overall method might be applicable to also non-corticosteroids, but this needs further work, and I believe that PBPK modeling of what's happening in the lung might be a more powerful and not so expensive way of testing that hypothesis.

DR. LI: Thank you.

DR. LIONBERGER: Any other questions for the speakers? Sid? Who is it for?

DR. BHOOPATHY: For Darby.

DR. LIONBERGER: Go ahead.

DR. BHOOPATHY: Darby, you had shared how to propose a new analytical method, but if I had to somewhat expand this to a new bioequivalence testing methodology, an example would be, say,

permeation testing, skin permeation testing, as you're proposing a methodology or reviewing the first few applications, there's still a lot of uncertainty in terms of the boundaries of the methodology, in terms of its reproducibility, how consistent it is, how to handle aberrant data, and how to maybe apply statistics to demonstrate some sort of equivalence or inequivalence.

How are these issues handled where there could be a guidance based on certain information, early information, from early adapters, but as you open it up to the population, you start seeing some limitations with these models.

So how does one go about -- one part of review could be you have rule based and second being product based. Right.

DR. KOZAK: I'm going to try to make sure I got your question correct. I think in the first one where you're talking about the development and then the potential implementation of a new method, sort of the boundaries to introduction and to uptake, and what we're looking at, I see one of the

big components there is early and often engagement through multiple processes.

The more the FDA knows of the method as well as experienced the method, and knows its potentials and limitations and is able to compare, the greater confidence. If you think of just implementation from laser diffraction now to dynamic light scattering, there's an initial boundary of, oh, you need to compare back to and understand. But as that becomes more ubiquitous and we understand that principle better, it becomes more just common.

I think any new method has that, and that's what I think we're doing here in this space, as well as other applications, the regulatory sciences, is getting that knowledge early as well as in depth.

I don't know if that directly answers all of your questions, but I think there are multiple facets that then can be engaged. One is just the preliminary, brand new proof of concept, and that is through suggesting that there's a method of

research that needs to be done, and then there's the research programs that can start where we have an open. Then as it is developed by a company and they have greater confidence within it, they can then present that in a more comprehensive sort of presentation through a pre-ANDA or other sort of way to engage.

Rob may have additional comments or other people may have additional comments, but I think early and often, and as well as we're all on the same page of that understanding; rationale, justification as to why, and initial new methods, always that you need to have a couple of questions of how does that compare to what's been traditionally done. I think there is a little bit of understanding there.

DR. BHOOPATHY: Thank you.

DR. LIONBERGER: Let's start our discussion. The purpose of this session was really for some comments we received from industry about there's a lot of new approaches that are being generated by the regulatory science program, both

on the analytical and the quantitative sides.

How do we effectively integrate them into our development programs and into our ANDA submissions? I'm interested in hearing -- first, let's focus on the analytical side, but from the industry representatives both on the panel but also in the audience. So if you're from industry and in the audience and you have some perspective on this, what are some of the challenges?

I think Liang's slide framed the question very well about what's the ecosystem for these new technologies, should look like, to say how much do you depend on there's a new method in the literature or there's a new method that has to be commercially available, and what can FDA do to help these implementations of this ecosystem in the analytical space? So open to comments on that.

DR. VALLANO: Thanks, Rob. I can take a crack at that first. Pat Vallano with Mylan R&D. Let me first say that, on this initiative, I really want to applaud the agency's work in this area. I think there's a lot of really good work being done,

particularly on the new analytical methods.

But thinking about it from an industry perspective and thinking about the question of implementation, talking about complex product and these analytical methods themselves, obviously many of them are very, very complex.

When it comes to method validation, which is a very critical element before one goes to implement, aligning on expectations around figures of merit, and I'm talking about methods maybe in an a PSG even, when it says do this type of analytical method. But understanding expectations early on about figures of merit, reproducibility, accuracy sounds relatively mundane, but I think that's very important, and how one goes about validating some of these very complex methods, it's really not straightforward.

We tend in many of these products to take an approach of see what the method can do, and then try to do some deliberate alterations and make sure that we can detect these. Sometimes we can do that, and the RSD might be 20 percent, and is that

good?

I think some of these points may end up adjudicating themselves in review, and if there was a way to perhaps get out in front, based on the agency's experience, working with some of these and coming up with some of these tools, where could you guide industry on what your expectations are I think could be helpful.

DR. LIONBERGER: Jim, any comment?

DR. POLLI: I'm an academic, so I don't have the same practical experience that you do, but the one observation I'd like to share is I have a laboratory, but I also spend time doing clinical research, and I observe tremendously different philosophies.

I think on the laboratory side, people have that curiosity, and it's like, okay, let's see what we can do and see if anything's there to be seen, and that sort of thing. On the clinical side, it's almost like, well, don't measure it unless you are guaranteed to use it to make a decision.

Just in my own working environment, since

I'm more of a basic scientist than a clinician, I always have to grapple with my clinical colleagues, saying, not everything is a phase 3 study. One question you had was how do you grow the ecosystem in a way. I think part of it is that, maybe growing an ecosystem where there's more analytical efforts.

I'm just kind of curious. I will just ask a question. I understand from Dr. Choe there was 90 pre-ANDA meetings or something like that. I think one or two industrial colleagues have told me don't ever tell the FDA anything that you're not sure about. I'm just kind of wondering how some of those things go.

DR. LIONBERGER: I would say I think that's not the right approach to take during the pre-ANDA meeting. I think that's an opportunity to -- the pre-ANDA meetings for the GDUFA program are designed to say, "I want to propose a new method." There's a scientific challenge and here's my product-specific, company-specific, confidential approach to this.

You won't get any value out of that meeting unless you share with us what the information is. If you don't share anything, we'll reject your meeting package. So you've got to have some data on the table. But that really helps because, especially there, you're going through this process because the industry wants to move the bar. I want to use a new method, so you have to provide some data that will allow FDA to give you some feedback on what will get that method to the point where it's helpful for a regulatory decision. So you really have to have the perspective of providing that information.

I think, here, the question for this group is what are the kind of things that FDA can do -- we do fund research. One of the examples from Darby's talk was the MDRS method. We fund research. In our lab, they use that method, and we believe that it would work.

What are the things that FDA can do to make availability of that faster to industry? What are the challenges in industry?

Are you able to buy the equipment? Are there vendors, or CROs, or contract lab organizations that can do it? Is that an important part of the ecosystem? What can FDA do to grow that ecosystem?

Should we have workshops on new technologies? The publications that we make from our labs, is that the key value point? What's the key piece of that, that we should be doing? Should we say, when there's new technologies, should we try to organize workshops around that?

Jim can comment, I think, on whether the CERSIs are a good experience in that. So Siva, your comments?

DR. VAITHIYALINGAM: Any new technology comes into the picture, Rob. It impacts the review timeline. The main objective we have is to get to develop a product and get the approval in a timely frame. We, in general, try to do it in given established techniques, established procedures, and analytical tools.

Any time new things come, a lot more work

needs to be done from industry and, generally, it's a lot more work for the agency to review, and ask questions, and get clarifications.

So that is it overall. It's a broad framework and putting it to what is the risk that industry takes. One thing that we could ask is, if there is a new technology that industry is proposing, is there an assurance that review can be done in a timely fashion?

DR. LIONBERGER: Yes. We have a user-fee agreement. You're guaranteed you're going to get your timely review. That's part of the commitment.

Here, our focus is what are the scientific aspects that we can do to help establish this process.

DR. VALLANO: I think anything that can be done to promulgate these methods and get them out into the public sooner. I think the publications definitely help. With PSGs, there might be more of a lag time before something finds its way in there, but definitely, the publications. Workshops, potentially you mentioned as well. Even outside of

peer-reviewed publications, potentially posting the methods in a white paper fashion perhaps on the FDA's website might be something that would be useful, too.

But I think anything that can get these out to help exchange that information from what the agency is doing out where the public and industry can see it, I think would be fruitful.

DR. LIONBERGER: Katherine?

DR. TYNER: I want to follow up and also signal Darby's point that the pre-ANDA program is a really nice way to get the discussion early because if there is a new analytical technique, the laboratories inside FDA are immediately put onto that pre-ANDA and then to start working on it.

So in terms of when that review actually hits us as a real ANDA, we already have that timeline where we've already started looking at it.

Then to your point about different ways to get these techniques in the public sphere, I would also recommend that people look at the standards organizations because CDER and OPQ is standing up a

standards recognition program, and you can take a look at the guidance that was published on that. That's another way that is a non-regulatory pathway to discuss and also to help standardize these techniques.

DR. LIONBERGER: Guenther, and then Bing?

DR. HOCHHAUS: Just one brief point; I think it's really very, very valuable to have the pre-ANDA meetings and discuss those new possible techniques. It was mentioned just before what quite often has been the question is what are the acceptance criteria?

For example, with the PBPK, what does it mean, verification? Do we have to be with predictions within the 80 to 125 percent or what other margins to really verify such a method?

The same is true for new analytical techniques, I believe.

DR. LIONBERGER: Bing?

DR. LI: Yes. I think, when industry proposes new novel analytical technologies, there are two questions they need to consider. One would

be what question these proposed analytical methods could address. Let me use this example to illustrate this request.

Budesonide inhalation suspension, everybody knows that this is a suspension product. Normally, a clinical endpoint study is needed. However, in the budesonide inhalation suspension, we recommend an in vitro package only. The reason is that, in the budesonide inhalation suspension, the insoluble excipient is only the API, so there are analytical methods available to compare the particle size of the API, which is the only insoluble ingredient in the formulation.

Then move to mometasone nasal spray. In the guidance for mometasone nasal spray, we recommended a clinical endpoint study. The initial thoughts was that, in the mometasone nasal spray, there are multiple inactive ingredients, insoluble inactive ingredients, in the formulation that mask the ability to identify the equivalence of the active ingredients' particles' equivalence.

So the key question is, can you develop a

method to identify the API particle sizing in the existence in other insoluble excipients in mometasone nasal spray? Then this NDRS, which Darby has touched upon, came to the stage to address this question.

That actually was the first point; if the analytical method that you propose would be able to address the key point that is needed to address the equivalence?

I think the second point, based on our experiences, in review of the NDRS method is the method validation part, the back and forth communications with regards to the method validation of this particular method that could adequately address the questions that we asked.

I would think the second thinking point of proposing a novel analytical method would be, could this method adequately address the questions as proposed?

DR. LIONBERGER: Thank you. Let's move on to our other side of the topic, which is the quantitative methods. Any questions or comments

from the panelists, especially from the industry side, on implementing new quantitative modeling approaches, PBPK, quantitative clinical pharmacology methods?

This just gets to Liang's questions at the end of his slides. What's most valuable in that space to the industry? Where are we now? Do we need guidances? I heard comments on verification and what's the standards for verification?

Is that the area that the panel thinks needs the most work, and what's your recommendation for the process? Should we have workshops around that? What type of framework should we use to develop those type of approaches?

DR. VALLANO: Yes. I think, from my experience in the generic industry -- and I think probably others would agree -- the quantitative modeling is not really one of the top things that historically has been in our toolbox for various reasons. I think as many generic companies are moving toward more of these complex targets, it's going to be increasingly important.

To help build the ecosystem, as was mentioned, there's always the risk of the unknown. Is it going to be accepted? The big thing is, well, we can make a model, but is FDA going to accept this for a generic application?

So I think promoting that ecosystem, and here's where I think workshops would be valuable to help really kind of foster that discussion. I think it's going to take a while and there have to be these steps along the journey. And even the discussion that we're having here today is useful, but I'm looking at it in that kind of way. It has to be a bit of a journey.

DR. LIONBERGER: Comments? Guenther?

DR. HOCHHAUS: I think it's really very important. Let's say you have a pre-ANDA meeting. You discuss alternatives, for example, modeling, and then you need to verify your model. I think all those things really need to be spelled out because I don't think that industry will -- like the situation, they seem to verify, but then the FDA says, well, that's not good enough, and go back

and do your clinical study. They would lose quite a bit of time.

DR. LIONBERGER: My summary of what the industry wants is industry wants clarity and certainty in the new approaches. I see lots of heads nodding in the audience.

With that, I think we will adjourn our morning session -- Sorry. Jim?

DR. POLLI: If I can just ask Patrick a question. If you had to say which was a bigger problem, a level of certainty or lack of certainty versus having people to do some of the examples that I think actually are evident in all the literature?

DR. VALLANO: That's a good question. I think it's more the certainty point because I think there are ways that we can go and find the expertise. If we don't have it in our organization, there are ways that we can go and find it. But I think at the end of it all, is it something that's likely to be accepted? So I would think, in my opinion, that would be the bigger

impediment.

DR. VAITHIYALINGAM: To just chime in what the gentleman said, in latest cyclosporine guidance, we have a criteria called earth movers distance. It is completely new for pharmaco industry, but what we found where the expertise lies. It is the organisms such as caterpillar uses that get distance and vary widely.

So we found expertise, and we addressed whatever questions they had in the BE guidance. Thank you.

DR. LIONBERGER: Liang?

DR. ZHAO: I just want to add in, if we talk about modeling, we are not only talking about a technique. I think the value is based on return on the investment from industry. For some complex products, you do feel that given the cumulative information from new drug development, also postmarketing stage, we understand the API formulation much better.

So can we glean the benefit from that knowledge? Modeling is not only bottom modeling.

It's to turn the data generated from new analytical approaches into knowledge that can be of regulatory use. If that's the case -- I also agree with model verification, that currently we are also thinking about which terminology to use, validation, verification. I'm not using verification.

That's also one of the keys, that if we think of the comment that we need to work on our clarity of the expectation from a regulatory agency, how to verify our model and how to make a model of regulatory use, I think we have some publications already.

In the coming CPT-PSP issue, there is commentary regarding how to validate and verify a PBPK model. We also published in the February CPT issue about using model-integrated evidence to facilitate generic drug development's review. You're welcome to take a look at those new thoughts from regulatory agency.

DR. LIONBERGER: We will adjourn the meeting. We'll be back at 1:05 for our afternoon session, so thank you all very much.

(Whereupon, at 12:06 p.m., a luncheon recess was taken.)

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

(1:03 p.m.)

DR. LIONBERGER: Hi. Welcome back, everyone, to our afternoon session. In the first part of this afternoon session, we'll be focusing on newly approved new drug applications that may raise challenges for the development of generic products.

We'll first have two FDA speakers to give their view landscape, and then we'll ask our panel and the audience for comments on what aspects of these newly approved products may pose challenges to generic products and what types of research approaches may be indicated from that.

Our first speaker is Lei Zhang. She's the deputy director of the Office of Research and Standards in OGD.

Presentation - Lei Zhang

DR. ZHANG: Thank you, Rob.

Those slides will be available online, so I will go rather quickly on those background slides and spend more time on the later slides.

As we all know, generic drugs in the United

States represent 90 percent of the prescription drug, and they only cost 23 percent of the standing, so it's a great cost savings. Among them, 30 percent are complex generics, but many of those complex products we know lack generic competition, and those are the areas our recent GDUFA research has focused on.

This is the GDUFA II commitment letter definition on the complex products, focused on complex active ingredients, route of delivery, complex dosage forms and formulation, and complex drug device combination, and some other categories where there's complexity.

Last year, following the public workshop, we proposed the FY 2019 GDUFA research science product areas, focused on 4 broad categories with 15 product areas, which I'm not going to go through all of them, but we know, among the 4 broad categories, 3 of them are very clearly associated with the complex product categories. The fourth category, we focus on the tools and methodologies that would cover both complex products and

non-complex products.

The first set of questions for the panel to consider is do these research priorities address the scientific challenges to developing generics of recently approved complex new drugs, NDAs, both new molecular entities as well as non-molecular entities? To aid in this analysis, we would review the landscape of previous few years of the new drug approvals.

This slide shows you the approved new drug application from fiscal year 2015 to 2018. The blue bar represents the total NDA approved in that particular fiscal year and the red bar represents the new molecular entity.

As you can see in general, new molecular entity represents about 20 to 27 percent of the total new drug approvals, and last year, we do see a big number of the NME with 30 NME approved in fiscal year 2018.

Among those new approvals, how many of them are complex products? This paragraph also showed the same 4 fiscal years, and the red area

represents the complex products. As you can see across those years, complex products represent a total of about 20 to 26 percent of total new drug approvals.

If you think about how many of them are a new molecular entity, from last year, last fiscal year, is 7 NME out of 40 complex products, and for non-complex, we have 31 new molecular entities.

Also, we already heard about FDA-developed product-specific guidances, which a lot of them are being supported by our GDUFA-funded research and science to identify the evidence needed to support generic drug development and approval.

New things under GDUFA II is we also have very specific GDUFA II goals in developed PSGs. In particular for the new molecular entity or NCE products, if they are non-complex, FDA will issue PSGs for 90 percent of them in GDUFA II, at least two years prior to the earliest lawful ANDA filing date, which means we will have those at PSG issued within two years of the approval.

As you are aware, GDUFA II started in

October 1st, 2017, so this year, on October 1st, some of them are hitting the GDUFA days, so we're going to monitor those PSG development for non-complex NME products.

For complex products, FDA strives to issue PSGs. As soon as we have a scientific recommendation ready, we can put in a guidance. Also, under GDUFA II, we have those pre-ANDA meeting mechanisms to interact with the applicants early on during drug development to help them develop those complex products if they don't have a PSG or if they propose alternative methods from the PSG.

Just a quick summary, in fiscal year 2018, we issued 208 PSGs and about 75 or 36 percent on complex products. I mentioned to you earlier the PSG goal for non-complex NMEs officially starting GDUFA II. We have been monitoring our development of PSG for those non-complex NMEs even prior to GDUFA II. As you can see, this graph shows you the blue represents the non-complex NMEs approved in that year and the red bar represents the number of

PSGs being developed. As you can see, we have met our goals to publish those non-complex NME PSGs within two years of approval.

For the fiscal year 2018, all of them will have goal days between October 1st of this year and September 30th of next year. So we will closely monitor the development of these PSGs, and we already have 8 of them published as of February of this year.

Now we are going to focus on those complex products, either as a new molecular entity or as overall, how the development of PSG is and what are the potential gaps and the signs in developing PSGs for those products, and how the regulatory science program can help us generate the data needed for the PSG.

This is just to show you the recent NME complex products from fiscal year 2015 to 2017. As you can see, we do have gaps. We have all NME complex products, PSG, NME being issued for those approved in 2015, but we still have 3 without a PSG for the product approved in fiscal year 2016 and

another 3 NME complex products don't have the PSGs.

So what are they? If we look against our research priorities, we found all three of those don't have PSGs associated with either complex active ingredients or complex dosage forms, and one of them is also a locally-acting product. But we do feel like we have a research program to cover those areas.

It is same for the fiscal year 2017. We have 3 NME complex products that don't have the PSG, and they all belong to complex active ingredients formulation or dosage form. All 3 of them are complex API, and also 1 of them is also a drug device combination product.

How about the PSG development for recent complex drug products? When we look at the fiscal year 2015 to 2017, NDA approval cohorts, as we see for the fiscal year 2015, 11 of them don't have the PSG; none of them a new molecular entity. For fiscal year 2016, 18 of them don't have PSG developed yet, and 3 of them are the new molecular entity I showed you in earlier slides. Again,

under the 17 products approved in fiscal year 2017, we don't have the PSG developed yet, and 3 of them are NME.

Now, I'm just going to focus on for those non-NME complex products approved in those fiscal years, what are the complexity areas and how do they link to our research priorities.

Among 11 of the products that don't have the PSG, 5 of them are associated with complex API oral dosage form; 3 are complex API; 2 of them are long-acting injectables. In terms of the complexity of the route of delivery, 5 of them belong to this category; 1 is the nasal delivery; 2 of them are inhalation products; 1 is topical; and another 1 is intrauterine products.

Again, we also see a big portion of those complex products that don't have PSG belong to the complex drug device combination category, with one of them implanted; one is the auto-injector; and another 3 is a drug delivery device. So we clearly see there's a need in this complex drug-device combination area.

For fiscal year 2016, similarly, we see 5 out of 15 belong to the first broad category with 1 complex API, 1 long-acting injectable, 1 abuse-deterrence formulation; and 1 complex injectable, and 7 out of 15 products belong to the complex route of delivery with the common route we saw as nasal inhalation, topical, and intrauterine.

Again, we also see 9 out of 15 comp products, which is 60 percent of them belong to the complex drug-device combination; 2 implanters; 3 auto-injectors; and 4 drug-delivered device combination.

In fiscal year 2017, we see also very similar categories where half of them belong to either complex API, long-acting injectable, complex injectables, or abuse-deterrent formulation; and 8 of the 14 belong to complex route of delivery; and almost half of them belong to the auto-injector or complex drug-device combination.

I just want to give you also some examples of what we saw recently regarding complex drug device products. This examples as shown came

out as a new device called a Respimat device. We currently have 4 new drug products approved with this device, and we do not have any PSG being published yet.

This is a new inhalation drug delivery device that is commonly referred to as a soft-mist inhaler. This device actuates a mist cloud of solution over 1.5 seconds, which is very different from other delivery devices. We have active FDA research towards development in the BE for standards for this type of drug-device combination products. You already heard some other challenges we face with other inhalation devices on the drug product development team early this morning.

The question to the panel is FDA believes that current research priorities address all of the scientific challenges we identified for those complex products through our survey of the new drug approval in fiscal 2015 to 2017 cohorts. The first question is, does the panel agree with this assessment? Second is, are there specific challenges that should be of higher priority?

Now, we're going to focus on last fiscal year 2018 NDA approval cohorts with regard to complex products only. So we have a total of 40 NDA-approved that are complex products. We have already developed 6 PSGs, and 7 of those are new molecular entity complex products. As of February, we already have 1 PSG developed, which is a topical product.

This table lists all the complex NME approved in fiscal year 2018, so in total there are 7 of them. As I mentioned earlier, one of them, we already have a PSG, and there's another 3 where research conducted in previous years has prepared us to develop PSG for those complex products, and we plan to develop PSG for those products in the next 12 months.

I want to highlight here at the bottom of this slide, FDA just launched a new PSG website to show a list of upcoming PSG that is going to be either developed as new or revised guidance for complex products. For those revisions, we also briefly state out the reason for the revision in

the next 12 months. We plan to update this website on a quarterly basis when we post a new batch of the PSGs.

Before I finish, I would like to show you a few examples of the complex products we identified from fiscal year 2018. This is one example of the complex API product called the patisiran. This is an oligonucleotide product that belongs to the complex API.

You will hear from the next speaker, Dr. Rodriguez. He is going to talk about FDA's lab that have those analytical assays being developed to address the assay to help us ensure the sameness if an applicant is going to develop a generic drug for this product. This is just to show you the structure of this new molecular entity.

Also, we also observed some novel or new drug-device combinations. This is just a new approach to treat nasal polyp disease. This is an implant that will be put to the nose, and we'll have extended release of the drug.

Also, another new drug-device product was

approved last year for sumatriptan to treat acute migraine. This is also a new drug-device combination which can pose its own challenge for developing a generic drug for those products.

The final question for the panel; do these products fit into our existing research priorities? Is there a need to adapt our research priorities to the change in the landscape of potential reference-listed drugs every year?

Finally, I would like to thank all the Office of Research and Standards staff, and in particular people listed on these slides who provide information for this presentation. I'd also like to thank you all for your attention.

(Applause.)

DR. LIONBERGER: Thank you, Lei.

Our second speaker is Jason Rodriguez. He's a branch chief in the Division of Pharmaceutical Analysis in OPQ-OTR.

Presentation - Jason Rodriguez

DR. RODRIGUEZ: Thanks, Rob, and I really do appreciate being able to present OPQ and OTR's

perspective on this. We see ourselves as partners in all this effort, and we're very glad to have a very robust relationship in collaboration.

Today, I'm going to tell you a little bit about the enhanced analytical tools for evaluation of complex generic drug products. Really, I'd like to start off by mentioning that OPQ has really a proactive science and research approach. The science program is designed primarily to focus on challenges that are in front of us; for example consumer complaints, public health issues. We see that right now with the valsartan and ARB studies that are going on that's publicly disseminated on the FDA website.

Our research program really does encompass a lot of generic drug science, and that research program is forward-looking. So we are constantly trying to keep abreast of new technologies and adopt new and emerging technologies for analytics and manufacturing within our portfolio.

This includes involving some of the new analytics, some of the new instruments, some of the

new technological advances because we'd like to keep the agency on the front edge of preparedness, so when we get those applications or submissions from firms, we're able to adequately review those.

Also, as discussed by Lei in the previous presentation, one big part of our portfolio in OPQ is forecasting generic drugs for newly approved NDAs and NMEs because, from a laboratory perspective, it's very important to set the foundation early on in the process so that when submissions are sent to the agency or questions, we're able to adequately evaluate those.

OTR plays a very important role in generic drug science, and I'll give you a little bit of high-level studies during this presentation. It really is going to be a whirlwind because I've only got 15 minutes.

One of the areas that we do quite a bit of work on is laboratory consults, and this comes to us through method evaluation. We call it method verification. We do that for new and generic drugs. And a lot of these are asked to assess

certain aspects of the method. So we don't do validation. We don't do verification on the whole analytical package. We're looking at only targeted risk-based areas that the review and assessment divisions highlight for us.

We also look at product quality that's pre- and postmarket. We do a lot of surveillance. We also are looking at pharmaceutical equivalence and adopting new bioequivalence approaches into our portfolio.

We do a lot of outreach for our review divisions and our assessors for training, and that's very important because one of the things that keeps the agency on the front end of preparedness is being able to maybe give reviewers either modernized or on-the-job training or exposure to some of these techniques. So OTR is very proud to be partnered with many of our review and assessment divisions in that.

Finally also, as has been discussed already, in guidance and standard development. A lot of times, we're asked to either provide

laboratory data or provide maybe an expert or laboratory analyst for one of the working groups.

Here are elements that we have seen already for PSGs, and I'd like to highlight the middle two as areas where the lab really does play an important role, and we're very happy to collaborate. That's on the analytical characterization of sameness and also on the development of standards for analytical characterization.

As Darby and Lei both said in their presentations, some of the areas that we are looking at and developing combined research programs, where we're developing protocols and trying to do forecasting, are in the area of complex APIs. That includes peptides and lipopeptides, and also polymeric compounds.

In the figure we show here is a study from 2015 where we're looking at glatiramer acetate and its comparator, the RLD and the comparator product. We use high-resolution LC-MS to show that the early elution times, we're able to differentiate between

the RLD and the comparator product. Also, we're looking at oligonucleotides and working on developing enhanced techniques for establishing identity and also in purity analysis.

We've already seen generic drugs are an important part. Ninety percent of the prescription fills are generic drug products, and we're all familiar with the standards of approval for generic, so same active, same strength, same dosage, and so forth.

But one of the areas when we are looking at complex generics, particularly complex active ingredients, complex formulations, complex route to delivery, and complex drug-device combinations is that it's very hard to apply those standard recipes for evaluation of those products.

One of the areas where OTR has done quite a bit of work over the last few years is in cyclosporine emulsion. Everybody knows that probably as Restasis. This product is very interesting because it really highlights two of the areas. It's both a complex formulation and a

complex route of delivery.

Here's the first case study, and I'll try to, whenever we have either published a paper or disseminated publicly some of these, to add the citation because I remember from the panel discussion earlier, that's one of the areas where industry was asking us how does this get disseminated and how is that information exchanged.

When we're looking at cyclosporine emulsion, one of the areas that we ask is what is the size and how to compare the size. In a study, we looked at a range of analytical techniques to try to find the particle size distribution for cyclosporine emulsion.

We see here the temptation is to try to compare across techniques and to try to compare the absolute answer. But the truth is that each of these techniques is specially suited to determine particle size distribution, and really, from an analytical perspective, the important part is to have all of these techniques at hand and take a holistic point of view when we're looking at

complex formulations.

Particle size distribution is very important because it affects the drug distribution and also the drug release. So I really do encourage you, as again, these slides are publicly available, to look at that paper that OTR was a collaborator in from last year.

In the next category, we have biorelevant dissolution. This is an area where we're trying to move from the traditional USP monograph methods for dissolution more towards being able to model what happens inside the body.

For these simulated GI contraction studies, we developed an apparatus, which is shown there on the left-hand side, that is able to provide simulated gastric contractions. One of the profiles of contraction is shown on the right-hand side, where there is a storage period, there is a mixing period, and then there is the actual compression force that is applied.

We used this approach to study nifedipine extended-release tablets, and we looked at two

different formulations. We looked at the osmotic pump, which is a reference-listed drug, and we looked at the polymer-based tablet.

If we look at the profile on the left-hand side for product A, which is the osmotic pump, we see that the gastric contractions, or the simulated gastric contractions, don't really play that much a role in affecting the dissolution rate on the bottom left-hand figure. But for the polymer matrix-based tablet, we do see quite a dependence on the role of simulated gastric contraction. So on the lower right-hand side, we see that the dissolution profile changes by quite a bit.

In the next area that we're also looking at a lot in OTR is trying to study the capabilities of using abbreviated impactor measurements as a kind of screening tool for the traditional cascade impactor methods. We looked at this with regards to orally inhaled products.

As everybody knows that has been in the industry for a while, the cascade impactor method is very time consuming. There are a lot of lab

hours that are devoted to trying to get answers.

What OTR tried to do, I think, probably started three or four years ago, was plan a study in partnership with OGD on using some of these abbreviated impactor methods. And those are pretty much shown on the right-hand side on the bottom. You can see, even if you're not familiar with inhalation devices, that the AIM is quite a bit more streamlined and there are less plates involved.

So what we've done over the last few years in OTR is conduct accelerated stability studies on three commercially available products shown here. For the two plots, we see the fine particle fraction for the range of impactors used, and we see that for the FSI and the FSI 2, the AIM methods do not provide really fully equivalent results as the full resolution impactors. That's one of the areas where we really do need to do a little bit more work, but this has been an excellent collaboration, and I think it's a good first step at trying to develop AIM as a QC tool, and one of

the areas where we will hope to continue working together.

The last case study I will show is on in vitro permeation testing. In vitro permeation testing is really used for topical and transdermal formulations, and trying to really measure the amount of drug products that flows through these systems.

In the lab, we have really two types of instruments. We have the Franz cell and the flow-through diffusion cells. One of the areas when we look at this in OTR, we like to keep a whole suite of analytical techniques, so we also look at the formulation using Raman imaging, and we are able to use quantitation using primarily chromatographic methods and mass spec-based methods.

Some of the areas where we have looked at this -- and this is a brief snapshot, but the citations are there at the bottom -- are on acyclovir topical cream where we looked at the effect of formulation on the manufacturing process

for the cream. We also looked at the API particle size distribution.

For estradiol, we looked at the effect of cold flow and really were able to get answers using these analytical techniques, and finally, testosterone gel, where we looked at the effect of permeation enhancers on skin permeation and flux.

In conclusion, I really do like to thank the panel for inviting OPQ and OTR's input on this. I think a lot of the laboratory aspects, we are very happy to be partners in collaboration. Really, it's one of the areas where, for the agency, we are able to, within OPQ, play an important role due to the capabilities of our laboratory.

Science and research are both important parts of, as I mentioned, OPQ's readiness, research readiness goals, and together, we can help promote the development of proactive tools to assess complex drugs.

Here's a list of the different areas where these case studies were contributed. I'd like to

thank each of those individual project leaders and really also say that this is really quite a feat because OTR is actually split in two different sites. We have a lab here in White Oak and another lab in St. Louis, which is where I'm based out of. So thank you for your time.

(Applause.)

Public Comment Period

DR. LIONBERGER: Thank you, Jason.

Before we begin the panel discussion, we have one speaker from the open public comment period, so Vinod Shah is representing the NBCD working group. Vinod?

Presentation - Vinod Shah

DR. SHAH: Good afternoon, and thank you for giving me this opportunity. I'm Vinod Shah, and I'm representing the Non-Biological Complex Drugs Group.

The Non-Biological Complex Drugs Group has the mission to ensure that the appropriate science-based approval and post-approval standards are created and globally introduced for the NBCD to

ensure patient safety and the benefit.

(Pause.)

DR. SHAH: I hope this is not counted in my time.

(Laughter.)

DR. SHAH: As Dr. Mehul Mehta indicated, it's a complex presentation of the complex drug products.

(Laughter.)

DR. SHAH: Thank you, Mehul.

Actually, what's happening is the rise of the biotechnology and the nanotechnologies have accelerated the development of the complex medicines. On this slide, you see the example of the small molecule as well as the complex nonbiological complex drugs, as well as the biological complex drugs, and these drugs are very difficult to completely characterize.

So what are the nonbiological complex drugs? Well, these are the products which are not homo-molecular in structure, but they consist of several compositions of very similar structures,

and this cannot be fully characterized, and a well-controlled robust manufacturing process is fundamental to ensure the quality and the safety of the product. In other words, the process is the product as far as the NBCD of the nonbiological complex drugs are concerned.

For the generic and the similar products, to be therapeutically equivalent, it is important that the product is pharmaceutically equivalent as well as bioequivalent so that it could be therapeutically equivalent and therefore therapeutically interchangeable.

But for the NBCDs, the major challenge is to establish the equivalency, either the pharmaceutical equivalence, or the bioequivalence, or both. Another challenge is the regulatory pathway harmonization between FDA and E.U.

Some of the recent developments in the NBCD areas also point towards the same situation, the complexity of the NBCD products, for example the GAO report which came out in January of 2018 also points out towards the scientific challenges and

are involved with the demonstration of the equivalence of the product.

The AAP, a guidance forum workshop, which was held last September, and the report just came out last month in April, also points out towards the problems with this and also emphasizes a harmonized regulatory pathway should be there.

Also, the very recent workshop, the FDA product quality research institute workshop in April, pointed out the similar things, and it was indicated that a biosimilar and nonbiological complex drug products should be approved based upon the stepwise comparison between the products, between the brand name and the generic product.

This slide shows the comparison of all the complex drug products. Again, at the bottom, you see the complex drug products identified by the agency. The green dots are the biological complex drugs and the blue dots are the NBCD complex drugs which forms a small group.

Actually, at present today, there are worldwide discussions with respect to how can we

standardize the process, how can we have a good regulatory pathway, and what should be the situation. You see that at least on this slide, the examples of the presentation, very recent publications on the European regulatory landscape of the nonbiological complex drugs, and also on the right side, you see the GAO report which identified the problems and the issues with the nonbiological complex drugs.

There has been these additions made even in Europe to change the legislation so that a better approach, a better pathway could be established. A similar thing has been also proposed by our commissioner, Dr. Scott Gottlieb, which indicated that we should contemplate on change the Hatch-Waxman construct to allow the agency to look at small complements of the clinical data in the context of an approved complex drug.

So you see that on both the sites, E.U. as well as the FDA's is thinking towards changing the legislation so that a uniform pathway could be established. Again, this is an example where the

commissioner has indicated in the latest ICH presentations, that maybe a standardized equivalence document should be prepared in order to have the approval for the bioequivalence of the complex products as well as non-complex drug products.

What would be a complex desired state that we would like to have? It should be having a science-based approach for the generic as well as the similar nonbiological complex drug products. We could call it as an NBCD similar pathway, one which should be universally accepted. We are looking toward the globalized harmonization of the scientific and the technical requirements for the generic drugs, so that everyone should be able to follow this; a stepwise comparison between the test and the reference products at all the stages to avoid non-comparability in the clinical studies and to facilitate the interchangeability, which will assure the therapeutic equivalence of all these complex generic drug products. We would like to avoid a non-equivalency in efficacy and safety.

How could this be achieved? Well, this could be achieved only with the involvement of the stakeholders that we can ensure a fit for the purpose of work. So it should be including the complete awareness, the understanding, and the alignment of all the parties involved together.

In order to really promote and discuss these types of scenarios and look at the nonbiological complex drugs, we are also going to be holding a workshop, and we would like to invite all the participants to come in this month, within 12 days, a complex medicine, science regulations, and accelerating development in New York at the New York Academy of Sciences on May 13th. Again, there will be more discussions on this aspect, and everyone is welcome.

Again, what I presented today is the opportunity probably for us to join hands together and try to develop a harmonized globalized battery so that everywhere, it could be approved by the similar situation. Thank you.

I finished in time in spite of all the

complex difficulties.

(Applause.)

Panel Discussion

DR. LIONBERGER: I'd like the panel members to introduce themselves for the afternoon session, starting with Lucy.

DR. FANG: Lucy Fang, associate director, Division of Quantitative Measures and Modeling, Office of Research and Standards, OGD.

DR. GOBBURU: Joga Gobburu, University of Maryland.

DR. LUKE: Hi. Markham Luke. I'm the director of the Division of Therapeutic Performance in the Office of Research and Standards in the Office of Generic Drugs, in CDER.

DR. MEHTA: Mehul Mehta; as I mentioned earlier in the morning, director, Division of Pharmacology I, Office of Clinical Pharmacology and New Drugs.

DR. POLLI: James Polli, University of Maryland.

DR. STIER: Ethan Stier, acting deputy

office director, Office of Bioequivalence.

DR. TEMPLE: Bob Temple, deputy director of CDER for clinical science.

DR. TYNER: Katherine Tyner, acting associate director of science for the pharmaceutical quality.

DR. ZHANG: Lei Zhang, deputy director, Office of Research and Standards in OGD.

DR. RODRIGUEZ: Jason Rodriguez, the laboratory chief in the Division of Pharmaceutical Analysis in the Office of Testing and Research and the Office of Pharmaceutical Quality in CDER.

DR. LIONBERGER: We will begin by asking if there are any questions for our speakers. I'd like to ask Vinod a question. You can come to the microphone.

You proposed alternative pathways for complex generics. Can you explain how you think that will expand access to complex generics rather than make it more difficult to provide access to complex generics?

DR. SHAH: There is a great similarity

between the biotechnological products and non-biotechnological products, only difference being that the biotech products are using the living organisms in terms of its formation, whereas the nonbiological complex drugs are made by chemical synthesis.

If you ignore that, everything else seems to be more complex in the same blinds and the same scenarios. So like for the biotechnological products, you are having a step-wise comparison, first looking at the chemical analysis, then looking at the toxicity, animal studies, preclinical studies, and then looking into the clinical studies, and making the comparison between the brand-name product and the test product.

So a similar approach could be followed for the nonbiological complex drugs and actually that is somewhat similar to what is followed in Europe in some of the cases. So our suggestion is maybe to follow a similar pathway, making a step-wise comparison with test and the reference product at all the stages so that we can avoid the

dissimilarity at any stages between the brand name and the generic drug.

DR. LIONBERGER: Thank you. Any other questions for the speakers?

DR. LUKE: This question also goes to Vinod. Doesn't lumping complex products with biologics complicate things even further?

I think, currently, we have generic drugs that are complex and non-complex. I think that's a sufficient kind of characterization of the lay of the land. To add in biologics into that complicates it even more. I think that's a problematic approach to the landscape.

DR. SHAH: Well, I don't mean to add the biologics into that. I'm suggesting to follow a similar approach; in other words making the comparisons of the test of the reference product at all the stages; not looking into the approach that you have already established for the biologicals, looking into the comparative clinical studies, small clinical studies for the two products, and that is what is not done in some of the NBCD

products which have been approved.

That's the reason why you see some of the problems that's coming up, especially like, let's say, for example, copaxone. The different methodology has been used for the copaxone. You are not following these. The product was approved not based on the in vivo studies in humans, but all the other studies.

So to avoid such things, it would be good to have a comparison, and other suggestions is to have a similar thing between Europe and U.S., everyone working together so that the same kind of regulatory approval pathway could be established.

DR. LIONBERGER: Let's move on.

DR. LUKE: That's an unusual twist to call it something like that, non-country rock-and-roll type of thing, a very unusual twist on wording.

DR. LIONBERGER: Let's move on to the panel questions, which focus on the newly approved NDA products, and an open floor? Any discussion for it?

DR. RODRIGUEZ: I can go ahead and start if

that's okay. I think one of the questions that was proposed was whether these research priorities do give a good landscape of some of the research and testing work that's done.

I think the answer from OTR's perspective is yes. We get some of these products and NMEs through our method verification program as a new drug site. These are all areas. I saw a lot of familiar and important overlap.

The lab's already been exposed to some aspects of the methods and some of the considerations that are taken by the review and assessment divisions. I would say that's a pretty good portrait of where we're at right now.

DR. LIONBERGER: One aspect that I noticed when I looked at the landscape that was provided was the prevalence of the combination products. I'd like the panel to address the question, for combination products; especially those complex ones, what are some of the aspects that you see are important to emphasize in our future research activities related to these new drug approvals?

DR. LUKE: I'll start. I think the combination here that we're focusing on, specifically a drug-device combination product, is an area that we see as very important and we're investing a lot of our research efforts and resources into exploring that area further. You can see that in the current call for grants and the current projects that are underway, thank you, in the Office of Research and Standards.

DR. LIONBERGER: Bob?

DR. TEMPLE: This question is going to just reflect my total ignorance of what you're talking about. My dim recollection of all this stuff is that if you believe the blood level tells you everything you need to know, you're done, and it's very easy.

The complexities arise when the blood level doesn't tell you, like every derm bioequivalence that actually has to do with --

DR. LIONBERGER: Everything that's on our list here is whether blood levels aren't.

DR. TEMPLE: So that's what we're talking

about.

DR. LIONBERGER: Right.

DR. TEMPLE: You're talking about where blood levels don't do it. Well, if that's the case, then don't you need a trial with either a clinical or some kind of pharmacologic endpoint? I mean, I'm just thinking of biosimilars, which I've had a fair amount to do with.

They all have to do studies. The study may be the clinical outcome or it may not be, but it's some pharmacologic effect. It's a little tricky because you have to do it somewhere steep, a steep part of the dose-response curve, or you'll miss important differences.

But is that what we're talking about, that you have to do a study that show that something happens?

DR. LIONBERGER: The standard for approval for generic products for bioequivalence, as you can imagine, is that we have enough evidence that the drug delivery to the site of action is the same. We can do that by blood levels. We sometimes do

that through looking at clinical data. But we also do it through looking at the in vitro performance of the product, and the drug delivery rate, and the comparison between the two products.

So a lot of the laboratory work and science on these more complex products is saying what's the delivery rate or the release mechanism from those products, and can it be measured correctly and accurately in the laboratory characterizations? So the in vitro approach is on the table as well.

DR. TEMPLE: You always have to wonder whether the in vitro method figures out how the lung works.

DR. LIONBERGER: Right, and that's why we're doing research in these different areas.

Jason, can you comment a little bit on, in Lei's presentation, she identified some new types of API that we really haven't seen before, so I'm thinking of the oligonucleotides and the anti-sense RNA.

Can you talk a little bit about OTRs, experience in characterizing those, and how well

characterized do you think are the NDAs, how pure are they, what kind of analytical methods has the lab developed or is developing for those types of new APIs that really haven't been seen in CDER-approved products until very recently?

DR. RODRIGUEZ: Right. I think that one of the areas that OTR is working on under the broad umbrella of oligonucleotidesis is developing a research program where we have stakeholders from several different areas of CDER, including OGD.

One of the areas and considerations, when we're looking at some of these complex APIs and complex drugs, is that there is a different point of view based on the office that you're from. When you're thinking about the laboratory studies, it's very important to capture and cast a broad net out to get those points of views.

From a laboratory perspective, once we harness what is the considerations from each stakeholder, then it's important for us to develop what is the path forward in the laboratory.

So I see, in a lot of these areas, the path

forward includes a combination of maybe advanced chromatography and also high-resolution mass spec work. That is one of the areas where we made a lot of investments in the laboratory to try to stay up to what's currently available. So that's one of the areas from a logistical point of view.

Now, when we look at these from the new drug arena, for example, and some of these do come to us from the method verification program, one of the things that we do look at is we do have discussions with the review staff of what are the areas that you are considering? We don't take these consults and just look at anything. We always are looking at a targeted area that the review divisions have asked us to focus on.

So that's an important piece of knowledge. It's in the knowledge bank of what are the areas that are being considered now, that we use then when we're developing these longer, I would say, three- to five-year research programs on how we developed the path forward. I hope that, in a roundabout way, answers the question there.

DR. LIONBERGER: Katherine, do you have comments?

DR. TYNER: I would just follow up and give a signal-boost, that the labs really are well equipped. One of the things that we try to get from the public input is what instrumentation that we need to be making sure that we have available and that we have knowledge of.

DR. LIONBERGER: Joga, and then Markham?

DR. GOBBURU: Just to be clear, the drug-device combination, the specific question is more about the really long, shall we say, acting --

DR. LIONBERGER: I think one category of products that we saw in this list was a very long-acting injectable. So these are implanted for up to 3 months at a time.

DR. GOBBURU: Yes. I can give you an example. Actually, from my experience, the longer the duration of release, the likelihood of establishing an IRVC is much greater because you are making at least the most rate-limiting step.

I have experience with IUD device, which is

for 5 years, and there is a very simple linear IRVC showing -- yet, the device can be changed, but I'm sure that the device comparison is pretty well established of what type of physical and chemical engineering characteristics comparison. But the coating and then the release, there are methods to accelerate and compare in vitro. We don't even need in vivo studies.

DR. LIONBERGER: Markham?

DR. LUKE: I just want to point out the beautiful juxtaposition of the two speakers and the topics that they talked about. Lei talked about the technological advances in new drugs, so each new drug, especially the complex products, present new technologies.

We're all for innovation and bringing new products to our American patient population so they can have good healthcare. But at the same time, in keeping up, we have new technologies for getting at microanalysis, getting at better and better adjudication of small levels of drugs, looking at incremental changes in drug concentration; for

example, doing subdermal concentrations of drugs with really tiny samples, and better than Theranos types of stuff.

So we're advancing technology to try to keep up with the innovation in new drug formulations and new drug products.

DR. LIONBERGER: Bob, do you have a comment?

DR. TEMPLE: I just wanted to ask you about your previous example. If you have a long-term drug that releases slowly, you still can rely on blood levels over time.

DR. LIONBERGER: So in that one, one of the approaches is to do blood level studies. One of the challenges that I think the generic industry would say is that those studies are generally not -- you generally can't do them in healthy subjects, so they have to recruit patients on those products for many of them, especially the long exposure times.

So that could be a barrier to recruiting the patients. Sometimes, when we have the

patients, you can't do the simple 1-dose crossover study. You have to sort of switch the patients during their treatment.

From the pharmacokinetic point of view, if you have a 3-month dosing interval and you want to switch them and let the new product come to steady state, sometimes you have to have a multi-year study. That's why I think, as Joga mentioned --

DR. TEMPLE: Especially if it's a 5-year --

DR. LIONBERGER: -- right, right -- that when there are in vitro/in vivo correlations that are used and sometimes been established, you know that they're possible from work that the new drug development has done, that that's an approach toward a bioequivalence method.

Often, those are the focus of our research activities to help develop the appropriate IV-IVC type methods.

DR. TEMPLE: I guess my initial response is the biggest problems where you don't really know what the relationship with the blood level is to what it does. One of the drugs that was listed

before was eteplirsen, where the approval was based on an array of increases in dystrophin in the muscle.

We have no idea what the relationship of the blood levels to that was because the response was hugely variable. I just wondered if people had thoughts about how they were going to do that.

DR. LIONBERGER: I think that's an injectable product. Right?

DR. TEMPLE: Yes.

DR. LIONBERGER: I think there's not a bioavailability question there. There the issue for the generic drug would be the same active ingredient and --

DR. TEMPLE: But it's a fairly complex molecule.

DR. LIONBERGER: Yes. And that's why the analytical methods have to be developed to characterize those more complex molecules.

DR. TEMPLE: But you think, maybe even if it's a complex molecule, blood levels might do the job?

DR. LIONBERGER: Yes, or again, generally for injectable solutions, we generally don't think we even have to because the bioavailability is going to be 100 percent of its direct injection or IV dosing.

Any other comments from the panel? Lei?

DR. ZHANG: Yes. I just want to go back to that drug-device combination. When we think about it, it's very complex because you have drug-device interface, which we have a lot of research on, but there's also user device interface, which I feel we probably still struggle a little bit, especially it depends on the design of the device and how a patient is going to interact with the device, and how we do appropriate comparison.

So I just wonder whether other panelists --

DR. LIONBERGER: I think Lei's question was about the human interactions with the drug-device combination, so the user interface or human factors question.

DR. GOBBURU: But I mean, for the device,

is it not a requirement for the device to be approved in the first place? I thought we'd have to do that.

DR. LIONBERGER: For the new drug device or for the generic?

DR. GOBBURU: Yes, new drugs.

DR. LIONBERGER: I mean, the new drug device has to be --

DR. GOBBURU: No, but the device for the generics is usually the device that is approved.

DR. LIONBERGER: No.

DR. GOBBURU: Not necessarily?

DR. LIONBERGER: No.

DR. ZHANG: They can have it different.

DR. LUKE: So there's variability in how combination products are approved. The combination product is defined as a drug and a device used in juxtaposition. The device may be part of the drug application itself, so you can actually have a device that's part of the NDA or you can have a device as part of a PMA or 52K that's reviewed separately by our sister center. But how those

products are used together is something that we look at.

DR. LIONBERGER: For example, like the inhalation devices, that's a device. It's a drug delivery device. It doesn't have to be identical in the generic versus the brand product. The scientific question is what are the characteristics between those two devices that have to be the same in order for it to be a substitutable generic product.

As Lei said in the first case, one aspect is the drug delivery rates, which are more or less measurable. You can measure them through the PK effects. You can measure them through the in vitro performance.

The other aspect of that comparison is how the user uses the device. What actions does the user have to take, and at what point do those potential differences become so large that the product you would not say are substitutable, and what differences are still differences but still allowed and wouldn't affect or impact substitutes?

That's the review question, and the OGD review staff has to deal with all these combination products, is if there is a difference in the interface that the user has presented, is that difference significant or not?

DR. GOBBURU: But to me, we already have policies for that. Right? You compared the within-subject variabilities. And if there is a product within subject variability interaction, and it goes, what is it, 2.5 or something like that, there's a problem. So we can apply the same routes.

DR. LIONBERGER: If you think that your drug delivery is the measure of successful use of the device, I think that's --

DR. GOBBURU: But the clinical trial will tell me both of them.

DR. VAITHIYALINGAM: It's not the question of clinical trial or equivalency. For the device differences between innovator product and generic product, it shouldn't cause any confusion to follow the labeling instructions in the original innovator product.

DR. LIONBERGER: In the bioequivalence studies, they're usually done under controlled conditions where you ensure that the person uses the device correctly. So you compare drug delivery between two cases where both devices are used correctly.

The user interface question, why it's more difficult, is if you're not instructing patients and they're just substituted, will they use it correctly? And that's a very hard question to answer.

DR. VAITHIYALINGAM: Both the devices have to have the same instruction of use. If the generic product has a different instruction of use, then it is -- it won't be approved in the first place.

DR. LIONBERGER: So maybe, Siva, you can talk about, in the generic industry, when you're developing these products, what are some of the challenges in matching the device?

If anyone from the industry wants to comment about that aspect of generic product

development, what are the specific challenges that you see as product developers in this area of products that have devices? And if you're not willing to comment here, I encourage you to make those comments to the docket.

MS. NEWCOMB: Hi. I'm Claire Newcomb from Mylan. I would like to encourage you to stick around to the next presentation because my colleague and I from Teva and Mylan are going to present on exactly this.

DR. LIONBERGER: So we may in the next panel be able to come back to this a little bit more. So Jim?

DR. POLLI: I'm an academic, so I don't develop generic products for a living, but just have some thoughts about my daily life. I'd like the initiative to have good instrumentation because it makes all the difference.

When I think about at least the time I spent, I probably spent at least about 10 percent of my time just trying to stay up with analytical methodology. I think we spent a lot more time than

we might think, and that's very important over the long haul. Maybe my major point.

DR. LIONBERGER: So Mehul?

DR. MEHTA: Just the general thoughts about Lei's presentation and then OGD, this mandated requirement of PSGs, especially for complex drugs. I think the OGD is focusing the effort in the right direction, and now we are collaborating even more and more on our new drugs and generics, or identifying these complex products.

The questions that you were asking are, these are all questions that are important questions that need to be paid attention to at the approval time, the new drug approval time.

DR. LIONBERGER: I think some of those also come up in the new drug to review as companies make changes during their development process that you and especially probably the Office of Clinical Pharmacology see and have to bridge through the development process.

DR. MEHTA: That sharing of information, knowledge, across our organizations, I think, is

getting better and better. I think, especially with the PSGs, that you have [indiscernible]. I just see that as a lot of good collaboration.

DR. LIONBERGER: I believe that we will have a break, and then we will reset for our final panel of the day. So we'll be back in 15 minutes.

(Whereupon, at 2:10 p.m., a recess was taken.)

DR. LUKE: Hello. Welcome back. Welcome to the afternoon session for the Generic Drug Workshop 2019. We have a speaker who exemplifies that good generic science does not know national boundaries.

Walter Wigger-Alberti is a CEO and clinical advisor for dermatology for Bioskin GmbH, and he's going to be speaking about specific challenges in the evaluation of irritation and sensitization for transdermal systems, a dermatological appraisal focusing on scoring and application. Walter?

Presentation - Walter Wigger-Alberti

DR. WIGGER-ALBERTI: Hello, and good afternoon to everybody in the room who I

unfortunately cannot see. I strongly apologize that I was not able to come in person, but I truly believe that this has a great value for the equibalance. I would like to thank Steven for the technical assistance.

The purpose of my presentation is to highlight the challenges for the current recommendations by the FDA for the application procedure and scoring in phase 1 studies with transdermals.

We all know that transdermals may cause irritant reactions due to their occlusive application of adhesive materials and sometimes even cause allergic reactions. So that is why they should be applied once daily on intact skin only. The application side is to be rotated daily. And any application should not be used more than once in 14 days. This is for patients and not intended to apply them repeatedly on the same skin area.

However, cumulative irritation is usually tested with repeated applications on the same skin area for topical drugs such as creams and

ointments, also under occlusion using test chambers. The reason is that we want to maximize skin response to early detect and to compare irritant potential of drugs.

A 5-day test design is only sometimes used before authorities may allow goal or no-goal decisions and to go into patient. But the classical phase 1 trial as part of the [indiscernible], however, is 21-day cumulative application with daily application or sometimes only 15 applications over 21 days, where the products stay on the skin over the weekend.

For the testing of the sensitization potential, we start usually with an induction phase, also over 21 days, but with only 9 applications in total because the test products stay on the skin for 48 or 72 hours. And after [indiscernible] for usually 2 weeks, the products are to be applied on a new test area once and the readings are performed over 48 or 72 and sometimes 96 hours.

During the challenge phase, it has to be

decided by the investigators if the reactions are likely to be irritant or allergic. Typical examples for irritation can be seen above with low levels of scoring and/or decrease of test reactions such as 2, 1, 1, 0.

Allergic reactions are usually stronger, stay longer, and they also increase [indiscernible] evaluation even though the product was applied only once. For example, as you see below, a score was 1 and then followed by score 2, 2, and even a 3.

Here, you can see a typical mild irritant reaction to a transdermal. It's a sharply marked erythema, some follicular spotty erythema. This is really a mild reaction. But on the next picture, you hopefully see the additional infiltrate and even some papules assigned for allergic reaction.

On the next picture, which is the next reading of the same lesion, you see even stronger, and on the last picture, on the last reading, you even see the edema is now crossing the [indiscernible], spreading over the area the patch was applied. So these are clear signs of an

allergic reaction to a transdermal.

Now we come to the problems with the current scoring. So far, the standard for the testing is given by the FDA guidance for industry, for skin irritation, and sensitization testing of generic transdermals. This has also been used as a reference for other topical drugs. Ointments and creams are tested almost the same way, and even the latest EMA guideline refers partially to that FDA guidance.

Now we are coming to the scoring system that is presented in that guidance. It's claimed to be a recommendation, but only a few companies are brave enough to use other scores even though, which I would like to explain, it is absolutely inadequate for topical drugs in general and for transdermal and special.

For any irritant reaction, the leading symptom is erythema, and the erythema increases with stronger irritant potential of the product to be tested. But the score here presented is not reflecting that. You may see that that's the score

with 1, which means minimal erythema, so that's now a little increase with the two definite erythema, but then it stays with erythema, and there are papules with a score of 3 or 5, edema and papules; 6 is just vesicular eruption, and 4 is only edema. There is no irritant reaction that increases, which will reflect a score from 1 to 7, absolutely impossible.

It's accompanied by another score which has caused other impacts, and the other impacts are focusing on symptoms as a result of dryness like scaling, cracking, peeling, and so on. But this is actually not seen in the application of transdermals, and I will explain to you why.

I actually was wondering where the score comes from and the Berger Bowman score that was published in 1982 for testing the irritant potential of cosmetic products, 150 cosmetic products, they wanted to compare 14 days' application with 21 days of application, but they suggested that 14 days are enough to discriminate topical products. However, this was news for

cosmetics, and they also themselves referred to an older publication that you could see on the next slide.

This publication from Lanman from 1968 in which also cosmetics were tested, but particularly bath oils and deodorants, products that have a high level of detergent that of course may irritate and they dry out the skin for which the other effect scores might be useful, but not for transdermals.

But who decided that this is an adequate score for topical drugs, and especially for transdermals, where each removal of the plaster itself removed also parts of the [indiscernible], corneum and causes any signs despite the other effect scores. So what we may see with the score can't be seen because the transdermal is removing it.

DR. LUKE: Walter, we have about 3 more minutes for your presentation.

DR. WIGGER-ALBERTI: That's very short. Okay.

(Laughter.)

DR. WIGGER-ALBERTI: On the next slide, we see the typical increase of erythema as the leading symptom of irritation. Next slide, this is just to show that with the patch testing, the erythema decreases. Edema is actually following the same, and scaling is increasing, but this is after removal of the patches over time. So it's totally different information and it's only typical for detergent. Sometimes, you get a positive control.

I would strongly recommend to use alternative scoring such as the score presented here, which is now also accepted as the score on the question and answer paper by the EMA. Another option is on the next slide. All these scores reflect the leading symptom of erythema that increases with higher rate and potential.

Now, we are coming to sensitization, where for the induction phase, we should also use the score with the leading symptom of erythema increasing, and on the next slide, for the challenge phase of the sensitization, we need something that, of course, is assessing the

erythema, but much more the typical signs of allergy, infiltration, papules, vesicles, and so on.

It is not possible for me, due to the shortage of time, to add another slide with a recent publication from this year from the Switzerland group, but they were using [indiscernible] as an additional tool to assess and measure irritant and allergic reactions, and they were able to show that irritant reactions caused an increase of temperature, but the increase of temperature by allergic reactions are much more higher.

So they were able to discriminate between irritant allergic reactions, and this was confirmed by an independent investigator who usually reads test reactions; so very impressive, and I think this is something where the discussion should be open.

I hope I have some more minutes for the application. You see that tape stripping using test chambers may cause strong irritant reactions.

On the back, you see the typical back a person where there were repeated applications of test testers. Whenever we renew for test testers, and this is the same as transdermals, we remove part of the stratum corneum, which will disrupt the skin barrier and may cause a lower level to induce allergic reaction or allergies.

On the next slide is publication demonstrating that tape stripping will increase irritant reactions. We can skip this, and the next slide is demonstrating the same for allergic reactions, and we can also skip.

We now are at the slide with an example of the rotigotine patch test. You see the results of the sensitization during the challenge phase. After 9 applications over 3 weeks in the induction phase, there were only minor skin reactions seen in the challenge phase, indicating that there is actually no higher potential of sensitization.

But the same product, next slide -- and I'm coming to the end -- was tested in the typical 21-day cumulative patch test, and here, you can see

that we have very strong reactions of the rotigotine patch close to the positive control. I can just say that many, many volunteers have to be discontinued with the application.

If you would have seen the reactions, you would have seen that these reactions have some symptoms of allergic reactions. I'm sure we would have seen positive test reactions if a challenge phase would have been added. For me, this is the reason why the 21-day approach with daily removal of transdermal should be re-discussed.

I'm coming to my final slide, the conclusion. The recommended score of the guidance and the application you see is not adequate for transdermal. The score has been developed for topical formulations, in fact, cosmetics.

The leading symptom for irritation is increasing erythema, and for allergic reactions, additional symptoms such as papules and edema are necessary, and the scores to be used should reflect this development.

Finally, the 21-day daily application of

transdermals may cause all positive reactions and even includes a higher risk for iatrogenic sensitization, and I thank you for your attention.

(Applause.)

DR. LUKE: Thank you, Walter.

We're going to switch out the podium. I'm going to introduce the next speaker from here. Our next speaker will be Lisa Nilsson. Lisa is associate director for the device RMB team at Teva, and she is going to speak about challenges faced in the development of the user interface for generic and biosimilar combination products.

All yours, Lisa.

Presentation - Lisa Nilsson

MS. NILSSON: Thank you very much.

I'm going to talk about the challenges faced in the development of the user interface for generic and biosimilar combination products. I'm going to focus on the device part and how the user, which could be a patient, or a nurse, or a doctor interacts with this device. In this case, the drug is less important, even though, of course, the drug

will have impacts on how people deal with the device.

In January 2017, there was a guidance released from the FDA about how to do comparative analysis and related comparative use, human factor studies for drug-device combination products submitted in ANDA. What this gave us was actually some guidance of how to do the whole usability and human factors process for generic devices. Before that, we had more or less followed the same process that we followed for our specialty product and tried to tweak it through the generics. But you're going to see that a very different approach is taken.

This guidance was released, and we're very grateful for this guidance. It was great to have it. It actually gives very useful and practical support on the development of generics, and it clarifies that the generic combination product is to be substituted without additional healthcare professional interventional training. So it's actually not that you have to be able to use all

the labeling per se.

It introduces three different types of threshold analyses and how to categorize the outcomes of them, and these threshold analyses are looking into labeling, comparative tasks, and on the fiscal aspects of the device.

They also have a chapter on the comparative use human factors study. So this is a study that would be intended to confirm the differences in labeling a device can be substituted with the same clinical effect and safety profile.

For a specialty product, there are also human factors studies, cold semi-table validation studies, but the purpose of them is to demonstrate safety and effectiveness, so it's a different type of study.

What do we do today? The typical process for human factors in the industry would be to follow this list, that first, you planned activities, you identify users, use the use environment operating principle. You identify and capture use and needs, describe how the product is

used, review any known use issues, complete the comparative analysis, would be labeling, task, physical; look into the use-related risk assessments, might do a comparative use human factors study, and then complete the documentation.

The first four steps are very similar to what we do for the specialty products. I think that most people in the industry would say, "We got this. We know how to do this." These four steps are still a big challenge for most of the industry and things that we discuss, all the things.

The first challenge we have is when we do review of known use issues. We have a generic device that we are developing, and we have the RLD. So we would then do different searches on the RLD and see what known issues there are.

The challenge we find here is, if the known use issues review shows that there are existing risks that originate the design or similar products that were on the market, how can we control those risks? Would this motivate minor design differences driven by risk control or do we have to

do an exact copy even though we know that tiny, tiny tweaks could make our device safer?

So this is something that we would like to have a discussion with the FDA on what this space is to do, looking at it from a risk perspective.

The next topic would be comparative analysis. This is when we compare the originated design with our proposed design in labeling, in the use of tasks, and in the physical appearance of it. We have to learn to examine all the external critical design attributes of the proposed delivery device constituent part in comparison to the external critical design attributes of the RLD.

When we do this comparison, we can come up with there's no difference. There might be a minor difference and there might be another difference. The problem here is when does a difference need to be confirmed in a comparative use human factors study and when another risk assessment is acceptable?

Even though the guidance tells us that, if you have no difference, it's likely not necessary

to do any other things. If you have minor differences and it doesn't affect your external critical design attributes, it will be likely acceptable if you have some data or information to support it. And if you have another difference, you should first modify the design, but we know that a lot of times, we cannot modify the design. At that point, they might request additional data or a human factors study.

The problem here for us is we know that some of these differences might drive -- even though we would put them through a human factors study, a human factors study is a simulated use study, so it's in a lab setting or similar.

We would only catch intentional use and the type of foreseeable misuse that will spontaneously come up in that study. In a lot of projects, we know that there are foreseeable misuse scenarios where we think that there might or might not be a difference, but we can actually not test them because some of these differences will only come up in misuse, for example, and how can we then make

sure that this is covered in risk assessments, and would actually other risk assessments be more suitable than a human factors study in this case?

The next step is the risk assessment itself. We followed design control, which means that we need to show that risk control and validation of user needs are done. A challenge for the industry now is, if we do a comparative analysis and we find the number of differences, how can we demonstrate in a satisfactory way that we have incorporated all of them in our risk assessments?

Do we need to follow a completely different process for risk assessments when it comes to generics or should we follow the usual process that we follow for specialty products, and then just add any comparative risks we find?

We would really like if FDA could share with us examples of what they have seen so far or tell us that we've seen people doing this that worked well, or we've seen people doing this and that didn't work well because this is a source of

endless discussions within device development, and the main goal is to make sure that our devices are completely safe and that we can prove it.

When it comes to the comparative use human factors study, we've decided we need to do one of those. Our big struggle here is how do we plan it. Human factors has always been a qualitative science, and in this new guidance, they talk about the comparative use human factors study as a noninferiority study. Suddenly, we moved from a qualitative science to a quantitative science, so we need a lot of things to be able to calculate the sample size. We need to have the acceptable deviance above the error rate. Should that be 10 percent or is it something else?

We need assumed error rates, but we don't know them until we run a study, so we then need to run a study just to calculate error rates to running a proper study and also which study power is required.

So when it comes to specialty, we get a lot of guidance on sample sizes. We would really like

more guidance from the FDA in this case on how large do our sample sizes for a comparative use human factors study need to be?

When it comes to challenges in the development of instructions, sometimes the IP is restricted, so we cannot have exactly the same device, for example, so our device will look different and have minor differences in aesthetics. How can we do that with the instructions?

Also, the IFUs are often outdated. We might copy a device that is 20 years old, so instructions for use nowadays might look completely different. We might have a different environment that we work in so people interpret things differently. What differences would be acceptable to make it more safe and effective for the user?

I have some examples of IFU design, so things that we would like to look into in information flow, device presentation, images, warnings. If all the warnings are at the end, maybe it would be better to have them mixed up in the instructions so we know that people actually

will read them.

Continuity and text; we also have an example of the information flow. In this example, the instructions tell you to unscrew the needle and throw it away together with a pen. And then, in a step later on, it tells you that you can also now put the cap back on your pen and keep it for the next use. We would like to rephrase this slide, please, so people don't discard a pen when they still have 27 doses in the pen. Can we do that or do we have to stick to exactly what the RLD has written?

There might also be examples in the IFU where we have images that might not be as clear as they could be, labels that they are. There might not be a picture of the device in the beginning of the IFU, something that I've seen that's a very good thing to do to orientate the user towards the device. For example, one device has a picture showing a person spitting. Do we need to include that? People know how to spit. We could focus the space we have on something more useful.

I want to say thank you to my colleague, Claire at Mylan for doing this. Thank you very much.

(Applause.)

DR. LUKE: Thank you, Lisa.

Our next speaker; we have Joga Gobburu, professor of pharmacy practice and science from the University of Maryland. He's going to be speaking on a potential role for innovative Bayesian and PBPK approaches to generic drug development.

Presentation - Joga Gobburu

DR. GOBBURU: Thank you very much for the opportunity. I really had two major points to make. The following is the background. Currently, there are certain products for which an efficacy study is required and to support generic approval. For these products, drug exposures cannot be measured or systemic levels deemed not to be relevant to the [indiscernible] or the local variability.

Several such products do not have generics, so if you go to the list of products on the FDA

website, you will find these. There is a serious need in terms of, from a patient's point of view, the cost. The agency, I think, is generally interested in solving that problem.

Some of the challenges are along these lines; one, the inability to distinguish between placebo. On top of that, then you also have to do noninferiority to the brand, and then of course, the patients. It's not that there are no companies who are attempting to do these, but most of them failed. That is the problem I'm trying to address.

It is generally accepted that drug levels are more sensitive than clinical endpoints. I don't think I need to convince this audience about that. But how do we potentially overcome this challenge of a clinical trial hurdle? Let's consider two cases: one, systemic levels cannot be measured. So this is a locally administered product and systemic levels cannot be measured.

The other is systemic levels can be measured, but because the law says it should be the rate and extent of bioavailability of the site of

administration, it has to be reflective at the site of administration, systemic levels are not used by us right now.

Let's say that systemic levels cannot be measured. The proposal I have is that, currently, a frequentist approach is proposed, meaning you would have to recruit patients, and then you use the clinical endpoint, whatever it is. And then you would have to show superiority over the placebo, and probably you'd have to show noninferiority of some kind of comparison with the brand also.

So the fundamental challenge here is that some of these medications, like for pain and so on, local, is very challenging to distinguish from placebo. Even for a new molecular entity, there are so many failed trials for these kinds of indications because the placebo is a moving target. Depending on who you recruit, the placebo responses are vastly different.

So in that case, then in the spirit of the generic rule, which is to make these products

available to patients at affordable prices, then there has to be some balance between that versus the low probability of distinguishing from placebo itself when we know that there is an active drug.

My proposal is we use Bayesian approach and borrow the strength from the other trials. It could be published trials or even the trials from the summary bases of approval. Then use that double delta, meaning we change from placebo and baseline, as a strong prior because those are registration trials. Those are like the holy grail for the approval of the drug. So there is no ambiguity, uncertainty. It is not like an opinion that you are asking somebody. It is reviewed by the FDA. It is within the files of the FDA, so the certainty of the prior information is very strong.

So I know that with great certainty I can use that as an informative prior to help both alleviate or bolster a little bit of support the differentiation from placebo, as well as in cutting down the size of the study. So that is a specific recommendation I have for us to consider.

Naturally, the Bayesian theory is not new, but application in the realm of generic drugs is something that we can seriously consider.

Now, what if systemic levels can be measured? Now, here is a proposal. I will try, as much as possible, to be very clear because it's a very subtle proposal I'm making.

Let us say that, through this research, we establish a PBPK model for a certain dermal product, shall we say. Because it is a dermal product, although you can measure the levels very well systemically, we don't want to use it because that's not reflective of the rate of absorption and variability.

So because now we have a PBPK model connecting the drug from its administration all the way to the systemic circulation, I now know the relationship between the local concentrations. What happens before the local concentrations is already taken care of. I'm not worried about that now.

The correlation between the local

concentrations and the systemic is biologic. It has nothing to do -- its meaning physiologic. It has nothing to do with the product itself because it is about the blood flow, the partitioning, and availability between the local tissue and the systemic circulations.

So I have to do that PBPK model only once. Once I prove the correlation between the local concentrations and the systemic, I throw the PBPK model away. I don't need it. I will use the systemic circulation just to do the bioequivalence, and I'm done. Otherwise, it puts a lot of burden on so many sponsors. Everybody has to do this PBPK or somehow access it, but why repeat the same signs over and over again? I already established the relationship. I will just use systemic levels for the bioequivalence.

This is a proposal where you have it reasonable. It doesn't need to be highly evaluated in my opinion for this purpose. It has to be a reasonable PBPK model, and that's my second proposal.

So that was it, and I yield almost 3 minutes back to the next speaker.

(Laughter.)

(Applause.)

DR. LUKE: Thank you, Joga, for yielding.

Our next speaker is Kiran Krishnan. He's the senior vice president, global regulatory affairs for Apotex. He's going to be speaking about demonstrating the U.S. reference standard and foreign reference standard sameness. Kiran?

Presentation - Kiran Krishnan

DR. KRISHNAN: Hi, Good evening. I'm here to talk about a specific research request, demonstrate sameness between the U.S. reference standard and the foreign reference standard.

The agenda that I will be covering today is specifically what is a research request, give you a little bit about the global regulator's perspective, some recommendations, and what are the benefits of the request that we're making. And finally, we'll close out.

Now, the specific research request is we're

requesting agency to conduct research to establish a criteria that could be used as a basis to demonstrate the sameness between the U.S. reference product and the foreign reference product.

Just to give you a perspective of what happens across the globe, what we found is there are two global regulators; that is, Health Canada and TGA that is in Australia. They both allow the use of foreign reference standard, and there are three general principles that they have considered.

One is the product is registered in a country with a compatible regulatory system. It's marketed in the country or origin by the same innovator, company or corporate entity, which markets the same product in their country. Of course, they also have a criteria that it should not be a narrow therapeutic index drug or require careful patient monitoring. Those are the basic underlying principles.

Now, there are actually published guidances in these jurisdictions. Just to give you a high-level overview of the Australian guidance or the

TGA guidance, it's much more broader compared to Health Canada, but what TGA says to demonstrate sameness is you need an assessment or comparison of the labeling on the product information between the reference product in Australia and the foreign reference product.

They need the certificate of analysis for both the reference product, comparative dissolution profile in at least 3 media, same nominal quantity of drug substance, same size, weight, and type of coating, physical chemical evidence that the products are quantitatively identical.

So as you can see here, it's a much high-level overview focusing mainly on the solid oral dosage form.

If you look at Health Canada, the guidance from Health Canada on this topic has specific requirements for dosage forms. If you look at immediate-release, they talk about, again, assessment and comparison of the labeling and product information; C of A's of the reference products; medicine ingredient is considered to have

high solubility and they are requiring that the products have same color, shape, size, weight, type of coating, and scoring conflagration; and the non-medicine ingredients are qualitatively the same; and ff course, they're asking for comparative dissolution profiles in 3 media.

They've also gone one level higher and they're looking at demonstrating the sameness for immediate-release orally inhaled dry powders. Again, in that case, they're looking for assessment of comparison of labeling, identical amount of medicine ingredient, C of A's of both reference products.

In terms of formulation, the expectation is the non-medicine ingredients are qualitatively and quantitatively the same within plus or minus 5 percent of each excipient. The physicochemical properties and in vitro performance are essentially the same, plus or minus 10 percent, and plus or minus 10 percent. And again, they're looking at device attributes. The device attributes, the qualitative and quantitative analyses of physical

and operating characteristics of the devices are same or similar.

Now, based on what we've seen with Australia and Health Canada, what we are recommending is the agency conduct research to establish a criteria that could be used as a basis to demonstrate sameness of the U.S. reference product and the foreign reference product for the following dosages, for soluble immediate-release, could be extended to modified release, including for complex products like products with complex APIs, complex formulations, complex route deliveries, and other complex dosage forms.

What are the benefits of this research? One is around public safety. You don't want to be doing the studies again and again for the same product. You end up doing multiple studies for different jurisdictions.

The other important part is timely development and approval of generic drugs and increased access to affordable medications. Now, obviously, when you try to do one study, you cut

down on the timelines that is needed for development.

One thing to also be noted is sometimes -- and the agency is very well aware of it -- it's very difficult to source some of the innovative products in the U.S., because obviously, they're in restricted distribution. In those instances, we find that products are more easily sourced in other geographies by the same innovator products.

So that is a need that the agency itself -- there's a big push from the agency to find out ways and means of solving the problems. We believe that this is one that could actually indirectly solve that problem.

Also, it supports global development now, and the agency has proposed -- actually, we want to compliment the agency for its proposal to ICH, where FDA submitted its reflection on further opportunities for harmonization of standards in generic drug development. This actually would probably help in that direction.

In summary, what we were requesting is, in

order to improve patient access to high-quality affordable generic drugs, this research outcome can provide industry with guidance on how to demonstrate sameness between the U.S. reference standard and the foreign reference standard.

Ultimately, what we are hoping is this research could enable a revision to the regulation down the line, which could allow the use of foreign reference standards for us to conduct bioequivalence studies to support the generic drug approval process in the U.S. Thank you.

(Applause.)

DR. LUKE: Thank you, Kiran.

Back to Rob?

Public Comment Period

DR. LIONBERGER: Yes. So now, we're moving to our open public comment portion of the session, so our first speaker in the session is Vatsala Naageshwaran from Absorption Systems.

Presentation - Vatsala Naageshwaran

MS. NAAGESHWARAN: Thank you, FDA, for giving me the opportunity to present at the forum.

Despite the presence of topical ophthalmics, there is a lack of genetic substitutes for conventional dosage forms like suspensions, ointment, and gels that can be attributed to the barrier imposed by the clinical endpoint in aqueous human PK studies that are currently required for bioequivalence.

A recent publication from the Office of Bioequivalence highlighted through a retrospective analysis of aqueous human studies differences in demographic data like gender, and race, and age, which influence the outcomes, the bias that was introduced because of the covariate imbalance -- and clinical endpoint studies, multiple speakers have spoken about the insensitivity, and especially where there's disease heterogeneity and demographic factors, you can have results that don't match within identical trials.

ORS has supported a lot of research initiatives to identify alternative approaches such as Q3 characterization to demonstrate structural similarity that can provide a fingerprint match of the physical-chemical characterizations to confirm

in vivo performance, and they have translated this into a subset of product as an option and a subset of product guidances.

The principle of characterization-based equivalence being the fact that pharmaceutical equivalence, especially for ophthalmic products, complex ophthalmics, doesn't always translate to therapeutic equivalence since Q1/Q2 formulations can have different physicochemical properties that can impact the in vivo performance of the product.

IVRT, which has been used to requalify an initially approved product following an acceptable change, is also utilized as part of this Q3 approach primarily for manufacturing tolerance to assure lack of process variability.

There are significant limitations with this approach. Since outcomes from Q3 testing can be influenced by methodologies, there is no established criteria for comparability, and importantly, neither Q3 nor IVRT have correlation to critical in vivo parameters like precorneal residence time and rate and extent of drug delivery

to the target site of action.

So illustrated in the slide are Q3 characterization data for a suspension product. We were looking at two important CQAs that are associated with topical ophthalmics, viscosity, which is an important critical quality attribute because it increases ocular bioavailability by increasing residence time. But the specifications for the polymers that are used for viscosification can be very wide, and this results in a range of viscosities that is obtained for different lots of RLD.

Additionally, there are multiple experimental factors that can also impact or provide different outcomes. And similarly, with looking at particle size, which is also an important CQA for a topical ophthalmic, we see several experimental factors that can bias the results.

A key question remains as to what is relevant. Is it the size of the native dispersed or the actual aggregated particles that are within

the product?

The FDA is keenly aware of these limitations. They have initiated efforts, as you can see on this slide, to support new research in multiple areas that include in vitro permeability across corneal and conjunctive barriers, tissue distribution, PK and PD models in nonclinical models, and ocular PBPK and PK/PD model development and refinement.

Absorption Systems has established and validated in vitro and nonclinical models to augment formulation characterization for close to two decades for the advancement and market approval of novel therapies for topical ophthalmics. We are completely aligned with FDA's efforts to take an integrated approach by incorporating functional assets for confirmatory evidence of therapeutic equivalence.

Complex ophthalmic products elicit biological activity by multiple mechanisms, which may not all be sequential. And in many instances, they have layered biology with early through

extended mechanisms of action that are dependent on formulation properties.

So when a drop of formulation is administered to the ocular surface, it interacts with the biomechanical barrier of the cornea before it can actually penetrate through the ocular surface. This interaction and permeation really depends on the transformation of the formulation that occurs on the ocular surface as well as the dynamic conditions that are present there.

So how do we recapitulate formulation biomorphology on the ocular surface given its criticality in determining bioavailability and efficacy?

Performance at the site of administration can be evaluated by IVPT studies using excised corneal and conjunctival tissue that can be predictive of in vivo bioavailability. In vitro studies using either rabbit or human cornea can provide significant information with regard to the rate of transfer, from the donor through the cornea into the receiver chamber; so absorption and

desorption rates that can be estimated that enables us to not only study the effect of various formulation characteristics on the permeability of drugs, but also to predict ocular kinetics in human.

IVPT, however, doesn't factor the surface dynamics at the site of administration, so retention or loss of product from the ocular surface. Rabbits are the preferred surrogates for topical ocular drug PK and PD studies because their eye anatomy and physiology resembles human, whether that's geovolume [ph] turnover rate, pH, of the tear fluid, or milliosmolarity of tears. It's very comparable to humans.

So you can evaluate the thickness of the tear film, for example, with optical tomography. You can measure drug levels in tears, collected using Schirmer tear strips. And these are all very useful ways to perform or monitor comparative surface dynamics between a reference and a test formulation.

Primarily, most direct route of drug

penetration into the anterior chamber is the cornea, but this is really only 20 percent of the ocular surface, and it presents a very tight lipophilic barrier.

A secondary route by which molecules can reach intraocular tissue is the conjunctiva, which has inverse properties to the cornea by being a leaky barrier. But most formulations are typically optimized to enable both ideal transcorneal and transconjunctival transfer.

We don't know the absorption distribution and elimination of ocular drugs in humans, so only a surrogate nonclinical model will provide a way to compare pathways that lead to intraocular distribution and the exposure that is necessary for bioactivity.

Modeling and simulations and the many speakers who spoke about this already in this forum, it's a very powerful tool to integrate this data across the in vitro and in vivo studies. Data from in vitro transcorneal permeation studies, PK, and tissue distribution, and PD studies can be

analyzed to develop PK and PK/PD models.

When combined with translatable assumptions, this enables sensitivity analyses of product-critical parameters and provides supplemental in silico qualitative confirmation of product equivalence.

A comprehensive approach of orthogonal measurements that incorporates early, intermediate, and extended formulation-controlled performance aspects, per the figure that you see in the slide, will provide increasing assurance of quantitative equivalence with supplemental support that is provided by the in silico PK/PD modeling.

Each successive quantitative assay that you see depicted in this schematic is progressively reducing layers of residual uncertainty driving towards confirmation of therapeutic equivalence.

This collective weight of evidence from all these multiple, orthogonal, and progressive measurements are basically essentially replicating the regulatory process of RLD approval to support the expected equivalence in human efficacy.

In conclusion, definitive confirmation of equivalence of topical complex ophthalmics can be provided only when Q3 and IVRT are augmented with biological assays that link API and formulation to their local performance; that is the in vivo biological effect of the site of action.

The augmented paradigm for equivalence, as you see in this figure, establishes a comprehensive product performance matrix where Q3 and IVRT testing can be standardized, but augmented with innovative and product-specific functional assays, bioassays, that enable a meaningful correlation of formulation function to in vivo performance.

We're here today because we want to mitigate the risks to support the approval of quality generics for complex ophthalmics. This would be achieved by using an in vitro approach that is augmented with biorelevant tools and PK/PD modeling that helps us to mitigate the residual uncertainty that is associated with product equivalence and strengthen the overall conclusion of bioequivalence of a test versus a reference

product. Thank you.

(Applause.)

DR. LIONBERGER: Thank you.

The second speaker in our open public hearing is Fubin Wu, representing GessNet Risk Management.

Presentation - Fubin Wu

DR. WU: Thank you, FDA, for the opportunity. First of all, I wanted to let you know I came from a different world. I hope that didn't scare you. I came from the device world, more engineer focused, and you eventually get into the combination product.

There is a method I want to introduce today, I think that can really help to solve many of the complex issues we talked about today. With that, I'm going to jump into it.

We provide the risk management consulting for the manufacturer of medical device and combination products. One of the common challenges for regulatory science, not only for the drug side of the device or even other agencies, is the

manufacturer submit data as required, and then the regulatory agency makes a decision, analyze the data, connect the dots, and make a decision.

What is the challenge with that? The challenge is that as the technology evolving becomes more and more advanced, new innovative solutions come to the world thinking about AI-driven solutions, machine-learning technology. Then the data become large and complex. So then that decision to draw based on a bunch of data becomes harder than hard.

There's one method, actually, almost particularly designed for solving that kind of problem. It's called assurance case. Think about a scenario where you have a bunch of data, and then you provide it, and say 100 pages or 400 pages, and the data is only getting larger.

You present to someone, whoever it is, and try to agree on what you try to present, which is whatever the desirable conclusion you want the reviewer to agree with you. You provide the data, but then what is the rationale of how those data

collectively are supporting the top conclusion. And typically in our regulatory framework, we do not particularly ask for that part of the information or that part of the information is not explicitly documented or provided.

So assurance case is the way. It is the argument. You can have 10,00 pages of data, whatever it is, and the assurance case can make the connection why those data are collectively supporting whatever the goal you try to achieve or for whatever the conclusion you want a reviewer to agree with.

There are certain terminology related to assurance case such as claim, which is really the conclusion you want a reviewer to agree with you; context; assumptions; argument, which is reasoning evidence, which is data.

I like this methodology because it really transforms data to be knowledge. Data without explanation doesn't necessarily become knowledge. It's just data. Someone has to review, analyze, and make the connection.

Here's an example of how, hypothetically, an assurance case can be. By the way, an assurance case can be a safety assurance case, security assurance case, effectiveness, and efficacy assurance case. It's just whatever the nature or property for a particular product or system you're trying to convey.

You can have a top claim in this example, combination product is adequately safe for its intended use, and then you break down into what actually that means. I want to just explain a little bit.

When we make that kind of claim, we typically do not have the luxury to have a particular testing report to say, because I have a test, this test report says it is safe. That's too simple, otherwise, we don't need an assurance case.

The challenge is complicated. What that means is when we say a combination [indiscernible] product is the same for the intended use, what that means is what actually constitutes sufficiently supporting that claim as true.

Then you break down into multiple criteria of whatever the criteria the agency and the industry can agree on. So you can say the drug itself is as effective for the branded drug, and the risk associated with the product is adequately mitigated. There may be other different things. Then we call that sub-claim.

The sub-claim can go further down to a level where you are able to connect your specific evidence. So we average down what is the claim, what's the explanation, and what's the data supporting your expectation. Those are the three key elements for our assurance case method.

Will you not be able to directly point the particular evidence supporting your claim, then you break that into multiple sublevels until you have specific evidence supporting that. Then collectively, you can build a case. You can convey that story.

How do we reason and how do we argue in general, which as we do all the time even with our thinking, we use logic. That's one way to argue to

explain something, or we use probability. There could be a scientific study or could be a statistical tool that concludes supporting you are correct. Or we use qualitative. If there are no other methods, then we do whatever we believe is right and let the others challenge why it's not, so that we likely use the qualitative approach.

There's also a concept confidence argument. When we break down from the individual claim to the evidence, that's where you actually can explain why is that. You say because this evidence is blah, blah. But then, on the other side, the confidence argument goes to how do you know that evidence is trustworthy, is scientific, is valid? We say that's the confidence argument for that piece.

So argument typically is explanation, why, and the other side is a justification why what you said is trustworthy. So when you break down from a top claim to a sub-claim, that's where if you have one claim, and you're saying we have met three criteria as a sub-claim, you need to justify why those three are sufficient to support the top claim

if every one of those individually is valid.

This is a general format. I did not particularly recommend you have to use a certain format. Whatever it is, the kind of thinking, how you can build a story to convey, I think is the real key, the learning you can get from assurance cases concept.

Some of the drug delivery devices such as infusion pump, the CDIH [ph] has actually implemented that assurance case method in the premarket submission. That is very much similar in many different ways to combination products on the device side of it. So your fusion pump is generally fusion. Drug delivery is typically a combination product delivery for a certain particular medication.

When we develop guidance on how to implement that assurance case, this is the overall argument structure. The devices are validated, verified, and the risks are mitigated, identified, and then it's adequately reliable.

This is an example. I don't have time to

go through it, but basically, as a result outcome, this is actually an HTML file. You can use a browser to open it. You can navigate through, and basically, there's a top claim and break down into the lower level. The reviewer can examine individual areas and search by keyword. You can even have a risk of distribution overall related area, and then search by keyword to do a review. This is a tabular format. It's another format.

One of the key lessons we have on the device side of the practice in assurance case method, one of the reviewers said, well, even the worst assurance case provide much higher quality data than non-assurance case submission.

The other thing is that it would have been very helpful on the device side if we actually have established structure of what do we call the sub-claim, or in other words, the key criteria, when we say the product is safe or effective, what that means.

Actually, because we practice in a way we provide whatever is being asked, and the agency or

the reviewer is making the determination, when that question is being asked, such as why the product is safe, you may not necessarily know the answer. What does a safe product mean for a combination product, for example?

On the other side, the reviewer can use a challenge case method, based on their knowledge, to challenge whether or not the assurance case submitted by the sponsor adequately addresses the top claim or whether the evidence is valid.

There are other things you can also read afterwards, but then this is an example for a hypothetical assurance case for the generic drug. I'm not an expert in the drug area, but just to throw an example to stimulate the thinking here.

The final thought, I would recommend an assurance case be considered as whether or not it's an ongoing initiative or anything new. I think assurance case can be a powerful tool for communication but also to really allow the industry to [indiscernible] by providing their own rationale, do their thinking, and for the reviewer

agency to actually do the check and balance.

(Applause.)

Panel Discussion

DR. LIONBERGER: Now we'll move to our panel discussion, so again, I'd like the panel to introduce themselves. Let's start at this end.

MS. VENTRELLI: Hi. I'm Molly Ventrelli. I'm regulatory affairs for Fresenius-Kabi in the U.S.

DR. STRASINGER: Hello, I'm Carolina Strasinger from the Office of Pharmaceutical Quality and the Office of New Drug Product.

DR. RODRIGUEZ: Hi, again. My name is Jason Rodriguez. I'm from the Office of Testing Research and the Office of Pharmaceutical Quality.

MS. RODY: Hi. I'm Beth Rody. I am senior director of generic clinical R&D for Teva.

DR. RANEY: This Sam Raney. I'm in the Division of Therapeutic Performance within the Office of Research and Standards and the Office of Generic Drugs.

MS. NILSSON: Hi, again. I'm Lisa Nilsson,

associate director for human factors at Teva.

MS. NEWCOMB: Hi. I'm Claire Newcomb, head of human factors at Mylan.

DR. MEHTA: Mehul Mehta, director, Division of Pharmacology I, OCP, New Drugs.

DR. LUKE: Kiran, you can come up here and join us here.

My name is Markham Luke. I'm the director for the Division of Therapeutic Performance in the Office of Generic Drugs.

DR. LOSTRITTO: Rik Lostritto. I'm the associate director for science in the Office of Policy for Pharmaceutical Quality.

DR. GOBBURU: Joga Gobburu, University of Maryland.

MS. D'AGOSTINO-FERLISI: Sandra D'Agostino-Ferlisi, global regulatory intelligence, Apotex.

DR. CONNER: I'm Dale Conner, director, Office of Bioequivalence in the Office of Generic Drugs.

DR. BROD: Bruce Brod. I'm a clinical

professor of dermatology at University of Pennsylvania. In Philadelphia, I kind of live in the clinical world. I'm the director of contact dermatitis and occupational dermatology, and I do a lot of diagnostic patch testing to determine whether patients have allergic contact dermatitis, so live mostly in the clinical world and see the challenges of trying to interpret positive patch test results on the skin. Thank you.

DR. LIONBERGER: For this session, because we have diverse topics, we're going to -- sorry, Kiran?

DR. KRISHNAN: Hi. I'm Kiran Krishnan. I'm the global head of regulatory affairs at Apotex.

DR. LIONBERGER: For this session, because we have diverse topics, we're going to go topic by topic and, at the beginning of each topic, you can then ask the speakers questions. We'll start with the irritation topic, and maybe, Markham, do you want to say a few words to start the discussion?

DR. LUKE: Historically, the serum

irritation sensation has presented some challenges. The 1999 guidance that was mentioned, I believe, was withdrawn, but continues to be used both in new drugs and in generic drugs as a way to look at comparing irritation sensation. It's old, it's antiquated, but we continue to use it.

Walter presented some of the concerns with it, and we thank Walter for that. But we continue to look for new methods to approach and look at irritation sensation.

We have Sam Raney. Can I pass the ball to Sam? And also Bruce, who has a lot of intellectual interest in this arena as well.

DR. RANEY: Thanks, Markham. I should have clarified that -- this is Sam -- I'm the lead for topical and transdermal drug products.

Is Dr. Alberti still with us? No, he's not. Thank you. On European time, okay.

Dr. Brod is with us, and perhaps there are others in the audience as well. One of the things that we'd be very interested in understanding is we understand some of the challenges with the existing

system. I think one of the key questions we'd like to get out of this session is what would be some of the research that you would recommend that we invest and what are some of the studies that can be done to take us from where we are today to a better way of evaluating this?

I want to break that out into two pieces of what does that better world look like, first, specifically focused on transdermal products, where we're trying to make a comparative assessment between two products, a reference product and a generic product, to evaluate whether the perhaps multidimensional aspects of the response that they induce, whether that's comparable or might be being noninferior, and how do we get to where we are from what we're doing today to that point?

Actually, a second dimension to that, that is not dealing with transdermal products but with topical products, topical generics, where the formulation of the generic product is different than the formulation of the reference product. What would be some efficient ways for evaluating

whether there is a potential implication for a difference in irritation or sensitization if these products are not evaluated in a clinical endpoint BE study?

Dr. Brod, I don't know if you'd be able to perhaps begin by commenting on those.

DR. BROD: No. Well, those are excellent questions, and I think it sort of highlights how our gold standard for diagnosing irritation and sensitization, which is patch testing, is fraught with a lot of problems. It's messy. It's subject. It's very subjective in nature, and I agree that we need more studies. We need to figure out a way to objectify whether a reaction is irritant in nature or allergic in nature.

There are various histologic type studies, but of course, that's invasive. But even that has difficulty sorting out some of the distinctions. Some of the infrared-type studies, I think, are interesting, and I think that would lend itself to something to study further.

One thing I want to point out that I think

is very important to try for you to understand is that irritant reactions, when evaluating new potential generic transdermal drugs that come to market, are far and above much, much, much more common than allergic-type reactions.

I very much agree that the rating system and the scale is something that should also be studied, and evaluated, and given lots of deliberative thought. Irritant reactions may occur relatively quickly. They're fairly reproducible, but on the other hand, there's a lot of distinctions between different skin types, different genders, the age of the patient. People react very differently. I think that's also an area that we need to study a bit further.

I think another area that we need to acknowledge is that we heard from our first speaker that redness is a pretty good indicator, but it's certainly not the only indicator of irritant reaction. So I think another area of study is to look and understand some of the different morphologies of irritant reactions.

We saw the old scale has a combination of redness on one side and lots of skin changes on the other side, and I think we need to understand how those two mesh together.

Those are just some of the challenges, and I definitely think we also need to -- the 21-day studies were somewhat arbitrary a little bit in nature, and I will take the institutional hit for that because a lot of those studies were developed by the great Albert Kligman, who was a Penn dermatologist who developed a lot of those studies at Penn. But I think those are subject to review as well. There's the potential to sensitize patients if studies are carried out over a prolonged period, and, as I said, irritation can usually be determined pretty quickly.

I think one of the things we need to keep in mind is that, in studying these drugs, if we sensitize somebody to the patch or the delivery system, we could be sensitizing them to the vehicle, but we could also be sensitizing them to the active drug, and then there's implications for

systemic reaction.

I don't know if I've answered your question at all, but the thing I wanted to at least put out there is that it's very complicated. I think I really appreciate the fact that there's going to be some deliberation over this and lots of moving parts.

DR. LUKE: Bruce, I want to thank you there. Also, as a practicing dermatologist, I agree with your concerns and also Walter's concerns that he raised, that the scale is, one, nonlinear, two, nonprogressive, the current scale that we use.

When we're comparing one product to another, it helps to have a progressive linear scale, whereas linear is possible, so that you can get some notion of bioequivalence. Right now, the scales are done, and the concern is that there might be some arbitrariness to it. Also the fact that it's antiquated and it's only done by a few specific centers around the United States that know how to do this, suggest it's fairly esoteric in nature.

DR. LIONBERGER: Maybe we can get the perspective from the generic industry on your sense of the sensitization irritation studies. What are some of the challenges you found in integrating these studies into a development program?

MS. RODY: Hi. I think I can comment a little bit. Just based on our experience, I will say that I do agree with the comments that have been made with respect to the scores, that they're antiquated. And I think just recently, as Walter pointed out in his presentation, new scores were adopted in Europe. They've also essentially removed the piece for the sensitization, the challenge phase, due to some of the ethical considerations associated with that.

One of the things, I guess, that I found in my experience is that the studies as they currently stand are not very sensitive. It's very rare that we see any of these studies fail, in my experience. Either it's the method itself or perhaps it's that we're not making such a significant change with a generic patch that it would make it more irritating

or there would be a sensitization reaction.

I even question whether or not -- in certain instances, depending on what changes are made to the generic patch, we have to keep within IIG, of course -- is there a real necessity to do these tests? So from my perspective, that's what I have.

DR. RANEY: That's helpful, actually. Are there certain areas -- you spoke about the, perhaps, lack of sensitivity. Do you have any ideas for the kinds of research that it would be worthwhile for us to focus on that would help us kind of generate the evidence to establish a new or different system?

MS. RODY: Sure. Yes. I don't have specific recommendations, I would say, today, but I do think it's an area of research that we should invest in with industry and with FDA. I think that there's a real need here because the studies themselves, as have been mentioned, they do have their limitations, and I would think that we could come up with some sort of a more discriminating

method. Unfortunately, I don't have something specifically to offer up today.

DR. RANEY: We have been contemplating research in this area, very much focused on the scales that I think all of us have spoken about, also looking at better understanding the underlying and molecular mechanisms, underlying irritation, and allergic responses; looking at the technologies that would be more sensitive to discriminating different types of mechanisms that induce irritant or allergic reactions using different kinds of spectral imaging that are more sensitive to differentiating these things; and also using better phrasing and logic to tease apart what contributes to having one score versus another score; and perhaps even having machine learning as more sensitive than a visual observer.

So if there's anyone else that has comments, we would welcome you to reach out to us independently and provide comment to the docket as well. This is an area that we're actively interested in researching and moving the needle

forward.

DR. LUKE: Rik has a comment.

DR. LOSTRITTO: Thank you. The comment I have is that you mentioned the IIG. I think in addition to the ingredients, it would be also good to correlate the impact of impurities, leachables, and extractables as well, because even though they may be present in very small amounts, it may contribute or even initiate irritancy or sensitization. So I would think research along those lines would be wise to include those sort of studies, too.

DR. RANEY: That's a great idea. Thank you.

DR. LUKE: Bruce might have something to add to that as well. Having been working in the cosmetics arena and also from the contact dermatitis field, if you don't have an ingredient in the product, you won't develop an irritant or allergic reaction to it. Right?

DR. BROD: No, that's very true. We're talking about reactions to kind of a complex soup

when they occur, and we're trying to brainstorm about potential, the holy grail, that will tell us this is the reaction, it's an allergic reaction, or it's an irritant reaction.

I think it's good to think along those lines, but I think it's also important perhaps to take a step back and think about maybe the way to discern whether reactions are irritant or allergic, is to be able to have a mechanism to separate out the individual components during the testing process, and actually have an easy way to test patients to those components, break it apart, and determine what, if anything, is causing reaction to occur.

Is it the active drug? Is it the vehicle? I think, in doing that, it will also elucidate to us, in many cases, whether it's an irritant reaction or a true allergic reaction. I think we need to break away from the old mold of doing defined readings and think also about doing readings over longer periods of time in certain subsets of patients as well because that actually

can be quite helpful in distinguishing between irritant and allergic reactions.

I think it's great to try to find that holy grail, but I'm not optimistic necessarily. We've been looking for it for quite a long time. And I don't want to discourage it, but I do think we need to kind of go back to what we do know with clinical experience, using some of those techniques and how we distinguish between irritant and allergic-type reactions. We struggle with this all the time, but I think testing the individual components might need to be a part of this.

DR. LIONBERGER: Dale, did you have a comment?

DR. CONNER: Yes. We actually have a history of doing something similar to this, and that's with the long and prolonged development of the vasoconstriction assay for steroids. Eventually, we came to adapt a method that was originally intended to measure erythema to do the kind of lack of color, effectively the opposite of erythema.

It started out also with all of all of its shortcomings as a human observer trial. That's the way it originally developed because the instruments and technology wasn't developed at the time when McKenzie and Stoughton were originally doing their experiments and publishing.

But we quickly became aware that, for these type of purposes, human observer ratings of 3, or 4, or 5 points, as Markham pointed out, it's not linear. It's an ordinal scale. The statistics on ordinal scales are always a little difficult, especially when you're doing equivalence.

I would say that a lot of that experience, even though it doesn't on its face seem to be exactly the same thing, should go into the thinking of what Sam said, a possible use of instruments or other technologies to read this rather than depending on the human.

Now, we all know that the human dermatologist eye is an extremely good instrument as far as clinical evaluation, years and years of training, and you all do an amazing job at

assessing clinical status of patients. But I think this requires a bit more technology. To get that linear scale that you're after, you really can't do that with human observer ratings.

DR. LIONBERGER: Let's move on to the second topic. So I want to move on to the topic of the device substitution question. Now I'll ask any panelists if they have any questions for the speakers that talked about the device substitution issues.

DR. KRISHNAN: I don't have a question but a comment on the issue that is related to -- there are certain things. For example, even we've seen some instances where the labeling may be the same, the steps may be the same, but then it comes back to subjectivity in determining the ergonomics or the differences in design.

I think any research work that could be done to make this more objective would really help because, right now, we invest millions of dollars in developing these devices. And then, if we have to start making changes to this, it becomes very

challenging. So that's something that could be looked at.

DR. LIONBERGER: So you would prefer a more objective measure of, these two devices are similar.

DR. KRISHNAN: Or a way for us to determine --

DR. LIONBERGER: Unambiguously.

DR. KRISHNAN: Yes, because right now, you're almost caught in the gray area, saying, is it okay or not okay, and then you wait.

Sometimes also, when we do these human factor studies in terms of analyzing the human factors studies, I'll redo the analysis. So yes, we send in control correspondence. We wait for the agency to come back and tell us. But as we see the number of products, in this case, that are growing, we would appreciate some kind of more clear-cut way to move forward.

DR. LIONBERGER: General agreement from the other members of the industry panel, that that's a desired state, to have more --

MS. NILSSON: Definitely. It would be easier -- it's hard to say unambiguous.

DR. LIONBERGER: Well, unambiguous could be it has to be exactly the same as the brand product. I'm not sure that's what you --

(Laughter.)

MS. NILSSON: That's not what we would like from a manufacturer's perspective, but the more guidance we can get, the easier it would be to focus our resources at the right place and making sure that we make the best and safest devices.

MS. NEWCOMB: I think, from my perspective, when you talk about ambiguity, we need to know what the question is. What is it that we don't want to have ambiguity on? There's a fine line between human subjectivity and no ambiguity. I think that's something that we really need to remember, that we can only understand what a human is going to do by talking and testing with humans, and that is very subjective.

DR. LIONBERGER: For the industry members, as you're developing these products, before you go

to the final decision, at what point do you integrate some initial human factors studies in your development program, like as you're choosing what device? At what stage in the development would you first do a human factors type of pilot study?

MS. NEWCOMB: I guess it depends on the nature of the project that you're developing and how much you know about that type of product already. But it would be very common for us to run early preference-type studies, understanding what the patient type can handle in terms of the device and what their needs are.

In a way, you're using your patients to define the needs of the product as well. But when we come to talking about more aligned with the new guidance, then there isn't so much of a requirement for us to look to human factors studies.

DR. LIONBERGER: Yes. So that's what I'm asking in your development process. Comparative human factors is sort of at the very end, but before you get into the guidance and the threshold

analysis, you are making some decisions. And that's the question; do you use human factors studies as a part of your design, product design and product development processes?

MS. NILSSON: We use human factors both as [indiscernible] reviews from the team, but there might also be early formative studies where we're just looking at preferences and similar and very early results. It could be a collaboration with marketing, so it's borderline market research, human factors.

But as I said, it really depends on what the application, who the user group is, et cetera. But I think every human factors group in the industry would like to be involved as early as possible in the development and be there when they say we're going to go with this device.

DR. LIONBERGER: So Rik?

DR. LOSTRITTO: I was intrigued, Lisa, by your comment, where you implied in so many words that if changes you were making were incremental to a device that made it less error prone, easy to

use, or labeling eliminated confusion -- I guess I would just challenge that a little bit and say you're dealing with two patient populations, those who have been using the RLD for a long period of time and new patients.

Let's say you successfully reduce the number of steps to use it from 10 to 7. It's not necessarily a given that reducing the number of steps is going to lead to better compliance. It may engender more errors of a different kind.

That is some of the thinking we apply when we're looking at that, so it's just something to put on the table to discuss.

MS. NILSSON: Yes, I totally agree that just because you have few user steps doesn't mean that it's easy to do. Sometimes, this could be much easier because it's more intuitive. So you also have to look at the whole landscape of devices and environments that the user is in.

We have a device that we developed 20 years ago. That was before we had iPhones, before people used their smartphones on a daily basis. So people

had a different mindset to different things. The whole user environment is different.

Then I agree, we have two user groups, the ones that are using the device already, and they should be able to use the new device without being retrained, so it should be intuitive. But I argue that if I give you a pen, and in some cases, you just take the cap off like that, or in some cases, you have to twist it off, you're not really going to notice which way you did it because those are both very intuitive ways for you to take the cap off a pen because you've encountered them so many times.

It's the same with a lot of devices we have, that in some cases, if I would go and ask a user, how do you do -- do you pull the cap off or do you twist the cap off? They don't even know. So if I give them another one with a different type, they wouldn't even notice the difference, or they will, intuitive, be able to use it.

In some cases, it would be a huge difference. But the biggest difference, I would

say, is when you have the new users. If we could have the possibilities to do minor tweaks to the IFU, we might not change any of the user steps, but we might add a tiny explanation sometimes.

There's a good example of, after you use the inhaler, you're supposed to tell them to rinse the mouth. If we just tell somebody to rinse the mouth, they would have been, whatever, they're not going to do it. If you tell somebody to rinse the mouth with water after usage, because otherwise they might get thrush, they're much, much more likely to do it.

So we wouldn't change the user step. We just want to add that little thing there, or we might want to move a warning from the end of the IFU. So you've done all your steps because you've followed your ST step by step, and then in the end, you realize here's a warning that says, at the beginning, I shouldn't have done a step 2.

If we could do those small changes, I think we could make the experience much more pleasant for the user in the end.

MS. NEWCOMB: I think that's the conversation that we'd like to have with the agency, is to understand that space in which we can make the user interface more current, more relevant to the user, without impacting the way that they use the device, or indeed, the reference product if they were to switch back as well, and that's something we have to be very cognizant of.

But there is an area that I think we do have to play with. And if you're very black and white and say everything has to be word for word the same, picture by picture, the same, then we're missing an opportunity to give the patient the best user interface that we can.

DR. LIONBERGER: Other comments?

DR. GOBBURU: Yes. So this latest discussion, to me, doesn't sound like a generic topic at all. It's a labeling topic. It has to apply for both the dosing device as well as this one. So I'm not sure if this is anything special there about generic approval. If the labeling language needs to be clarified, but the picture

needs to be in color instead of black and white, that applies to both products.

DR. LIONBERGER: Dale?

DR. CONNER: I had very similar comments, that a lot of times, when you're doing generic drug development, you could do a lot -- because you're years newer and you have newer technology and newer approaches, a lot of people, when they go to make a generic product, could make a much better one than the innovator.

But that's not the point. If you do really go full bore in making something much better, chances are, you won't be approved because you will have deviated so much from the generic product that you won't be acceptable. It would be probably a great NDA, but it's not a generic.

The other question I had was that you presented a very nice kind of very ordered way of engineering and science of this new product that you're designing. But when you go down the kind of optimal path through your steps, I just wonder how -- you mentioned IP considerations, but how

often does that kind of change you to a less optimal path through your development?

We all imagine the patent issues are always a problem, especially with devices. How does that really affect and constrain you proceeding through this well-ordered kind of design philosophy?

MS. NILSSON: I don't have any statistics on it, and I work mainly with sterile injectables. But I would say at least in 50 percent of the times, we cannot choose a device that is as similar as we would prefer to be sure that we could just sail through it, but because it's IP restricted, we have to go something that is slightly different somehow, so it's quite often. That will force you to do slight changes to the IFU because there are no options.

DR. KRISHNAN: Even if it's not the IFU, for the exact same reason, there are copyrights or patents, as a result which then you would need to tweak the shape. There could be, like, minor tweaks. And that's where it becomes a challenge for us.

DR. VENTRELLI: Yes. We do similar, syringes, auto-injectors, and I would say, when you look at something as complicated as an auto-injector, almost 100 percent of the time, they're covered with an entire thicket of patents that you have to get around and have to make changes.

Simple syringes and those things are a whole different story, but from an auto-injector perspective, you absolutely have to design around all the patents, and you have to start that at the very beginning so that you know what kind of an auto-injector to go for, and you can design your user needs to fit that in the rest of the design verification and validation.

DR. LIONBERGER: Any other?

DR. BROD: I think the other thing, too, to think about going forward, one of the disadvantages of the skin is you can see it. Somebody takes a pill, a branded pill and a generic pill, and one causes a little more stomach irritation than the other, you're not going to notice it.

So I think one of the things that I would just urge to think about going forward is what constitutes clinically meaningful irritation on the skin, and then try to develop a scale that reflects that as well going forward. I don't have the answer to that now, but I just throw that out there as well.

DR. LIONBERGER: So any further comments on the device topic?

(No response.)

DR. LIONBERGER: Then let's move on -- Kiran has a presentation on bridging and globalization, so any clarifying questions for Kiran's presentation?

(No response.)

DR. LIONBERGER: I have a clarifying question. If you're able to get enough product to do bridging, how different is that from the amount of product you need to do the full bioequivalence testing on the product from the U.S. market if it's just a -- something specific in that case, where it's access to amount of product?

DR. KRISHNAN: if you look at the -- like, for example, for the purpose of doing bridging, you probably can get away by doing dissolution work and characterization work, you don't need that many samples, but when you go through a bioequivalence study, you need not just a sample, but obviously the ratings as well. It's almost 5x of the sample that you need.

For what you need to do, looking, testing, you need 5x so that goes in rating. So you need a lot more for doing a BE study in those instances.

DR. LIONBERGER: In some cases, it would be possible to obtain enough samples to do a bridging study, but it would be a significantly less burden than obtaining the number of samples you need to do a whole BE study?

DR. KRISHNAN: That is correct.

DR. LIONBERGER: Rik, question?

DR. LOSTRITTO: Two questions. One of the things I worry about in the sequential thing like that is a phenomenon called creep, where if you have this product equivalent to the next, and the

next, and the next, little changes accumulated over time, and it won't be equivalent to the first one. I'd ask you how you would deal with that issue.

Also, in one of your slides, you said to be media dissolution. I hope that does not include surfactants. And if it does, how would you justify that to show equivalency when surfactants really normalize out so many factors?

DR. KRISHNAN: If I understand your first question, you're talking about the shift. Again, these are instances where you're talking about an RSB that is available in the U.S., and the same reference product is available in Canada by the same manufacturer. We have seen, in many instances, for some of these newer products that are coming out, some of these complex ones and the newer ones, they don't have different formulations in different markets. It's the exact same product made to the exact same cycle.

So those are the specific products. I mean, I'm just giving you one of those examples, but if you look at the guidances of the

requirements in Canada or in Australia, that is exactly one of the requirements. You have to demonstrate the sameness of the product.

That probably would take care of your first question. And I'm sorry, I missed your second one

DR. LOSTRITTO: I'm sorry. You mentioned dissolution 3 media.

DR. KRISHNAN: Yes.

DR. LOSTRITTO: That's a blanket statement. That could be a good thing or it could level out changes that are important, depending upon the media, and so forth, and other conditions.

DR. KRISHNAN: But you are just comparing the same two products, so again, these conditions are based on the requirements to do the multimedia dissolution profile.

DR. LIONBERGER: Dale?

DR. CONNER: I have actually a question about Canada and Australia. You've held them up as jurisdictions that are similar to the U.S., except for in references for what they considered generics. Even though they're similar, their

systems, and their regulations, and their histories are not necessarily the same as the U.S.

DR. KRISHNAN: That is correct.

DR. CONNER: I think, when you kind of throw them up as examples and say you should be doing exactly this, one of the things we were constantly getting into, I think you mentioned, international harmonization as well, is that a lot of countries that seem very similar and have similar ideas about the science don't necessarily have the same regulations. In fact, that word "generic" doesn't mean the same thing in a lot of countries as we have it here in the U.S.

So even though they are superficially similar, there are sometimes very little things that kind of are differences, and they may be not insurmountable differences, but difficult differences to overcome.

So if you're trying to harmonize a lot of these countries, sometimes they have to change regulations or even laws, and that's not a small matter. Having been involved just in the U.S. and

changes in regulations, it's a good 10 or 15 years sometimes for a major regulation change, so there's that.

We've had experience in the past -- I don't know how it is today -- where the same company, the same RLD company or big pharma company, produced allegedly the same product with the same name, but they were different. They contained the same drug substance or substances. They may have even been manufactured in the same factory, but they were clearly, by the company's admission, not the same thing, and so we discovered that only much later.

So how do you deal with those kind of things where you're assuming same company, same brand name, same drug substance, manufactured in roughly the same place? How do you provide assurance? If you're a generic sponsor and you don't have access to any of their secret, proprietary information, how do you go about assuring regulatory agencies that you're really using the same reference?

DR. KRISHNAN: I think that's a great

question. I think that's part of what we are requesting that the NC look into this issue to see if there's an opportunity to use or determine what is the criteria to establish that sameness, if you may.

Now, to your point, if there are differences -- I mean, obviously, these guidances dictate a battery of tests, and the expectation is these tests would be able to highlight the differences, if any. Again, that's something that again is more product specific and it's not something that could be applied in --

DR. LIONBERGER: I want to link this to something that came up earlier in the day. We were talking about BCS class 3 drugs, and the question of deformulation technologies. I think there is a linkage here between the type of things that you're asking on bridging and the technologies that someone would use to deformulate a -- I want to find out if I'm Q1/Q2 to a BSC Class 3 drug.

So I would appreciate some of the comments on the industry on your skill at deformulating

this, and also maybe Jason from DPA, because I know that you guys do some forensic-type testing on some of the biostudy samples to detect products, to show that they're different.

I'd appreciate comments on the state of the art of deformulation and forensic analysis and analytical methods of, say, solid oral dosage form products. So please?

DR. KRISHNAN: Obviously, deformulation itself is a huge science or activity that happens these days. Now, there are techniques that are available today. Of course, we looked at MDRS as one of the examples earlier, but then you have Raman spectroscopy, fingerprinting that's there.

Now, the deformulation is something that the generic industry does. Now, obviously we talk about the solid oral dosage forms, but that is something that we do as a standard practice for ophthalmics and nasal sprays because that's the basis on which we asked for the Q1/Q2 correspondence.

Now, solid oral; from our experience, we do

believe that there's enough solid state characterization tools available out there to understand not just the qualitative composition, which is obviously known a bit more importantly than the quantitative composition.

DR. LIONBERGER: Jason?

DR. RODRIGUEZ: From the FDA lab perspective, some of the areas that we have dabbled in as needed, based on different projects, analytics, in addition to Raman, which has already been mentioned, there is SCM Raman. There is also cyro SCM. So a lot of these microscopic techniques and morphology have been mentioned a couple of times.

Truly, since it's both a physical characterization and a fingerprinting technology, it's something that is really powerful when you're looking at some of these, and you're looking at ophthalmics, also transdermal drug delivery systems.

One of the areas as far as laboratory testing goes as well; since it was discussed

earlier, maybe there's some product out there, some residual solvent in the manufacturing. We've also looked at residual solvents of transdermal drug delivery systems as well.

From a laboratory perspective, one of the things that we care a lot about actually is, at first, begin given a target of what are you looking for as opposed to having a wide range of things you could see, because then it leads you off a different and winding path.

But the technology is there so along as we have an idea of what we're going to look for, what property, what ingredient, what impurity, so in that nature.

DR. LIONBERGER: Any other comments on the bridging products topic?

(No response.)

DR. LIONBERGER: So let's move on and talk about the application of Bayesian methods to generic drug analysis. I'm not sure we have the complete experts that we need to give full comments on, but I want to give the panel at least some time

to ask Joga some questions about this. So Markham?

DR. LUKE: Yes. I have a comment. You mentioned that, using the ANDA studies as a prior, one of the fundamental tenets to using Bayesian approach is that the priors have to be declared, a priori, that you're going into it with Bayesian approach. So quite often, an NDA may have led up to it; the two registration studies may not have been the only studies.

So a Bayesian approach usually takes into account the totality of all the studies that were conducted, including the failed studies. And the failed studies would then have to be factored in as priors as well, and plus the lack of a priori declaration would lead to a concern of using those NDA registration studies as priors; just a comment along those, and if you want to respond, please.

DR. GOBBURU: My specific proposal is the FDA says that, whatever you want to do, do it and accept that criteria because, otherwise, it'll be chaos for every company to compute that. They can come and negotiate it like any other guidance, but

the FDA has to put their foot forward on that one. We can argue about it. We need probably a detailed session. Everybody, when they talk about Bayesian, they keep, oh, what about the failed trials? What about the failed trials? They had no bearing on the approval because you're approved based on the efficacy, not based on the failed trials.

So even in the decision-making, you have looked at it, but you have not weighed on the lack of efficacy from those trials, so how can you use that against somebody else now?

We can argue about the technicalities, but if generally that idea is appealing, to me, it's worth pursuing because we're talking about research opportunities. We're not talking about changing the law.

DR. LUKE: If I could respond to that, I think the issue about Bayesian is that it's the totality of the evidence that leads to a Bayesian approach as opposed to the non-Bayesian approach where you're allowed to start a new study afresh, and you're looking at p values specifically from

that study or the two studies that you're getting at for registration. You can send in the other study if they will look at it, but the fact that you failed in the p value does not factor into the registration piece.

DR. LIONBERGER: Dale and Mehul?

DR. CONNER: There were a lot of things that confused me about your talk, and I think a lot of it was that you seemed to be mixing up NDA and ANDA concepts.

So one question is, if you're developing or trying to get a generic drug approved, and you're going to use NDA data as your prior, as your Bayesian prior, how do you get right of reference to that data? Because that data belongs to somebody else, and as a generic sponsor, that owner is not going to be very cooperative because you're essentially taking away their market share. So they're not exactly going to hand over the rights to use that data.

DR. GOBBURU: That's why I said FDA will set the rules. You do set the rules by giving a

guidance saying that you want 80 to 125, you want this kind of in vitro, you want F2. Those criteria are set by the FDA. What is wrong in being specific about the prior that a sponsor can use to design their trial and drive the statistics?

DR. CONNER: You would have to get access from the owner. We don't have any choice about that. If you were a company, you've designed and produced a product. You've paid for the studies that get that product approved. You own that data. And the FDA has access to it, but we don't own it. We can't just use it for whatever we want.

DR. GOBBURU: But most of those studies are published, too. You don't need individual data. Why do you need individual data? I have the mean [indiscernible] and the variability, and these details about the design. I can develop product from that.

DR. CONNER: I've had the privilege over the years of looking at data that was submitted to the FDA, which we have access based on our function, have access to everything, including the

ability to go in and inspect, look at the original lab books, or data, or whatever, computer data. I've also seen those same studies published in peer-reviewed journals, and the two studies don't look anything alike. When you look at the peer-reviewed information, you just simply focus on the positives and act like the negatives don't exist.

That experience of working at FDA has made me very -- I don't want to admit this in public, but has made me extremely distrustful of peer-reviewed data because I know it's the same study done by the same people, but it doesn't look at all the same when you have access to all the data.

DR. GOBBURU: So tell me this. How did you get the partial AUCs from [indiscernible] without the brand data? When we come up with a guidance for using a partial AUC for a complex or modified release product, where the heck would you get the --

DR. CONNER: We're looking at individual

sponsors --

DR. GOBBURU: No. This is before generics were approved.

DR. CONNER: Yes.

DR. GOBBURU: So you have to rely on RLD.

DR. LUKE: Can I put a positive spin on Bayesian?

(Laughter.)

DR. MEHTA: I've been waiting this whole day for some discussion on this. No. To somewhat on Dale's line, we do say the overall findings of safety and efficacy of a new drug, a general knowledge that can be utilized by the generic industry, and that's how we approved generics. So are you suggesting that, within that framework, this information also benefitted from that category, and then say that you don't need to worry about legal challenges or ownership of data?

DR. GOBBURU: Well, yes, because if we are not convinced that the availability of a particular product is of public health concern, none of what I said applies. If we're talking about -- I'm

talking about nontrivial, serious indications where there is a need for the generics and something has to be done for those.

DR. MEHTA: I clearly hear you, and the scientific part of me really gets excited, but we need to get our lawyers to just say yes to some of this. The other part quickly is changing the second half of your suggestion, but if I understand correctly, you're saying that, through PBPK or some methodology like that, you established surrogacy.

DR. GOBBURU: Yes.

DR. MEHTA: Then once that is established, then forget about asking for same surrogacy demonstration again.

DR. GOBBURU: Yes. That's right.

DR. MEHTA: So that is again going back to the line of question or concern that Dale is expressing. Who owns that?

DR. GOBBURU: Hold on. No, no. Hold on.

(Crosstalk.)

DR. GOBBURU: Any 505(b)(2), including cardiovascular, for example, you don't ask for CHF

studies for 505(b)(2)'s? You demonstrate angina, you demonstrate blood pressure lowering, and I will give you all indications.

DR. MEHTA: Yes.

DR. GOBBURU: Where did you get the rate to use the correlation from the original NDA?

DR. MEHTA: So again, that determination was made and that relied --

DR. GOBBURU: It's the same legal expectations as far as I can see.

DR. CONNER: There is kind of a legal difference when 505(b)(2) -- this was discussed a lot, I think, in public and probably amongst FDA, when 505(b)(2)'s first started to become popular, that the 505(b)(2) uses the FDA finding. They don't reach into the application and take the data. They use the FDA decision, which is of course public, as their basis.

They are not allowed to use whatever data they want out of somebody else's application; in other words, reaching into the application, picking out data, and using the study. They used the NDA

decision on that.

DR. GOBBURU: I am glad we are talking about this. Then you guys come up with a path such that for those kinds of needy products where the hurdle of proving to be a generic is very high, open that by saying that a 505(b)(2) type path is okay? Right?

Closing Remarks

DR. LIONBERGER: So we are coming to an end, so I thank everyone for the discussion. I think the last point illustrates that for generic drugs, there's this very complicated, scientific, and regulatory interplay that we have to navigate as we figure these things out, but that's part of what we do across all of the things related to bioequivalence.

We'll definitely have more discussion as we look into this area further, and I think we want to have maybe some more specialized discussion with a broader group of people who have some deeper expertise in this as we discuss this further. I think that's a great suggestion for something to be

thinking about.

So it's now my responsibility to close out this meeting, so I'd like to express my appreciation for everyone in the audience, both the people here in person and those on the webcast, we're very appreciative of your interest in this topic and your attention to the presentations. And we hope that if this has spurred you to have any comments, that you go ahead and submit them to the docket. You have about one month left for that docket, for your written comments. We value those written comments, so please submit them.

I'd like to thank all of our speakers, both from inside FDA and our external experts, for providing very triggering, very challenging, thoughtful discussions. I'd like to thank the panelists for participating in this and really showcasing the challenges that face the interface between the science and the regulatory aspects of generic drug development. I think that's what makes it consistently interesting to work here, and I think this discussion is very helpful to us as we

try to formulate what our research scientific priorities are going forward.

This is a meeting, and I'd like to thank all of the staff in ORS that really helped organize this meeting, like Stephanie Choi for leading the organization of that, making sure of all the logistics work, getting all of our speakers, and our rooms, and all of the staff in ORS who volunteered and participated to run the AV logistics, to run the check-in desk, to prepare the binders for you. All of that is staff from my office who worked extra hours to make sure this happened, so I want to give them all a round of applause for their effort in making this meeting be very successful.

(Applause.)

DR. LIONBERGER: The other FDA staff who made the logistics are the Great Room staff that have this wonderful room available for us and make everything work very smoothly for us. I thank also our communication staff and OGD for helping publicize this meeting within FDA and externally.

So what we're going to do is take back the comments from this meeting, the comments to the docket, and internally within FDA formulate our regulatory science priorities for the next year. You'll be seeing the results of this posted in the fall.

As I look at this meeting, I think there are a lot of interesting things that I think will be showing up in there. I saw a lot of questions related to various aspects of the excipients in the pharmaceutical formulation. They showed up in our questions on the solid oral BCS products, the fed bioequivalence study questions, the analytical methods to characterize the excipients in complex products, as well as the excipient effects on the transdermal irritation and sensitization.

So I think one big theme that you take away from here is the attention that we have to pay both as product developers, but as regulators, and our scientific understanding to those inactive ingredients. Certainly excipients is maybe better terminology in the product, and I think that's

something, and we'll be thinking about how to integrate that into -- because I think we also already have research that touches on a lot of those in a lot of areas, but to be more explicit about those aspects of important issues related to that.

The other thing I noticed is a lot of questions about the devices, both the delivery mechanisms and the interfaces for the drug device combinations. As we look at the landscape of the newly approved products, a big chunk of those ones where we're still developing our standards or have some device component to them. So that's an important aspect to really work on, both the science of the delivery and the interface is so much the takeaway.

Also, there's a lot of interest in the newer modeling simulation data analytics methods. We heard that in our Bayesian discussion here, developing the ecosystem around that, questions about method verification, validation, how to provide clear pathways for how companies can use

these in their submissions with the appropriate confidence in FDA that they're doing the right thing in the model; so lots of things to take home from here.

Again, the docket will remain open. Please send your comments in on these issues as we're going forward, and I would like to thank everyone for their participation, and now, the meeting is officially closed. Thank you very much.

(Applause.)

(Whereupon, at 4:28 p.m., the meeting was adjourned.)