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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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 very warm welcome.

2 (Applause.)

3 **Opening Remarks - Sally Choe**

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

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

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

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

1 130 grants and contracts and has established
2 extensive collaborations with various FDA
3 laboratories and offices.

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

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

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

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

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

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

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

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

22 Earlier this year, FDA approved the first

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

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

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

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

22 The support through the GDUFA research

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

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

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

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

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

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

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

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

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

9 (Applause.)

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

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

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

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

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

1 in those areas.

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

8 Again, as Sally mentioned, the GDUFA
9 research is critically important to our whole
10 generic drug program. It helps inform all of our
11 product-specific guidances. The new aspect in
12 GDUFA II of the pre-ANDA meetings, we got about
13 90 requests in the first year.

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

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

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

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

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

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

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

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

19 **Presentation - Sid Bhoopathy**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 (Applause.)

15 DR. LIONBERGER: Thank you very much.

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

18 **Presentation - Siva Vaithiyalingam**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 In this case, there are 12 excipients

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

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

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

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

1 in selection of the excipient.

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

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

14 (Applause.)

15 **Panel Discussion**

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

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

1 Bioequivalence.

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

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

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

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

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

14 DR. BHOOPATHY: Sid Bhoopathy, Absorption
15 Systems.

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

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

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

1 of Research and Standards in OGD.

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

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

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

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

22 I have one or two other questions, but

1 should I go with them or wait?

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

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

14 DR. BHOOPATHY: Right.

15 DR. LIONBERGER: Closer into the
16 microphone.

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

20 DR. LIONBERGER: Go ahead.

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

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

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

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

17 DR. LIONBERGER: So Siva?

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

22 DR. BHOOPATHY: Yes, in Central America and

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. VAITHIYALINGAM: Rob, I'll take the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15 DR. LIONBERGER: Not listed in the label?

16 DR. VAITHIYALINGAM: Exactly.

17 DR. LIONBERGER: Jim?

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

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

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

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

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

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

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

1 is, it is both mechanistic and empirical.

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

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

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

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

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

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

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

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

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

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

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

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

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

7 DR. KIM: Sure.

8 DR. VAITHIYALINGAM: Thank you.

9 Emilija, you want to add something?

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

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

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

4 DR. LIONBERGER: Gregg?

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

13 DR. LIONBERGER: Sid?

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

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

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

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

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

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

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

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

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

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

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

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

12 DR. FREDO-KUMBARADZI: Yes, majority.

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

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

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

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

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

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

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

16 DR. LIONBERGER: But I'm talking about the
17 reference product dissolution rate. What if you
18 had a reference product dissolution rate that takes
19 20 minutes? Is that a barrier to your use of a BCS
20 class 3 waiver? That's not under your control. I
21 mean, certainly, your product you can formulate to
22 make it dissolve very rapidly.

1 DR. VAITHIYALINGAM: That's a good point.
2 I remember it vaguely. There was one product where
3 we had this challenge. The FDA was okay with that,
4 the reference part being not within 15 minutes
5 requirement. But yet, the test product was within
6 15 minutes, so I believe agency was okay with that
7 justification, and we moved on with the busiest
8 biowaiver requirements.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 differences within low.

2 Do you have any experience where excipient
3 effects, say, don't affect moderate low
4 permeability but do affect low-low permeability?
5 Dr. Seo mentioned risk assessment. Is there any
6 risk assessment to be considered in thinking a
7 little more specifically about this range from 0 to
8 85 percent?

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

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

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

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

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

13 **Presentation - Arian Riedmaier**

14 DR. RIEDMAIER: Thank you.

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

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

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

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

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

17 This has resulted in approximately
18 50 percent of approved drugs between the years of
19 2011 and 2015 utilizing either salt or a complex
20 formulation approach. Of course, this opens up a
21 really novel opportunity in terms of modeling and
22 simulation as well, where we need to capture these

1 kinds of mechanisms and formulations.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 bioavailability that was measured was 5.4.

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

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

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

22 While there's a lot of value to a

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

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

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

22 The vision for this group is that

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

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

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

22 Where models have been verified with

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

5 (Applause.)

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

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

11 **Presentation - Amitava Mitra**

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

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

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

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

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

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

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

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

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

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

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

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

13 So where are we with this? So BCS 1's and
14 2's, again, a majority of the BCS 1 and 2
15 molecules, unless it's a very high first-pass
16 metabolic compound which goes a very high
17 first-pass metabolism, we know with fair confidence
18 that it's a gastric emptying and solubility
19 dissolution enhancement which affects food effect.

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Even the recent 2019 draft food effect

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

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

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

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

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

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

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

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

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

7 DR. LIONBERGER: Thank you.

8 (Applause.)

9 Our next speaker is Gregg DeRosa from Teva.

10 **Presentation - Gregg DeRosa**

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

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

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

1 stomach.

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

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

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

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

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

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

22 We collapsed the categories into what we

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

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

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

1 passed.

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

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

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

22 Some brief summaries and suggestions; we

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

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

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

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

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

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

10 (Applause.)

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

13 **Presentation - Zhanglin Ni**

14 DR. NI: Good morning. Thanks for the
15 opportunity. Today, I'm going to spend about
16 10 minutes discussing the scientific gaps that
17 impact the prediction fed BE studies.

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

1 events are anticipated under fed conditions.

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

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

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

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

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

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

22 Second, the model must incorporate

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

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

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

22 Then we can take a look at the solution

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

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

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

1 condition.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 (Applause.)

2 **Panel Discussion**

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

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

15 DR. NI: Actually, in this GDUFA-funded
16 research, actually, in this study, we only look at
17 1 API, which is posaconazole. Currently, we cannot
18 expand to other things at this point. This one is,
19 yes, API with low solubility.

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

22 DR. LIONBERGER: Seeing no clarifying

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

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

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

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

1 then applied it to different formulations.

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

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

12 DR. LIONBERGER: Yes, Jim?

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

18 Could you elaborate more about that?

19 DR. DeROSA: Which slide are you talking
20 about?

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

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

3 Can you just elaborate more about that?

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

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

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

22 So again, it comes down to fasting as being

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

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

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

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

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

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

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

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

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

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

10 DR. LIONBERGER: Bing?

11 DR. LI: Yes. My question is actually
12 along with Rob's comments. For that 5 percent of
13 cases where the fasting study passed and the
14 fasting study failed, are there any considerations
15 to exclude the formulation factor as well as the
16 inactive ingredients factors to conclude that
17 5 percent failing is contributed by the insoluble
18 or poor solubility of the active compound?

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

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

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

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

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

1 you found in the new drug to generic drugs arena.

2 DR. DeROSA: I understand, yes.

3 DR. LIONBERGER: Sid?

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

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

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

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

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

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

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

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

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

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

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

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

1 in a way that our reviewers can use.

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

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

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

1 study.

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

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

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

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

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

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

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

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

22 DR. LIONBERGER: First, and then MJ.

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

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

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

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

3 DR. LIONBERGER: MJ?

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

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

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

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

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

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

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

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

1 DR. VAITHIYALINGAM: During the initial
2 phase of development, all these things are taken
3 into account. For example, if you look at the
4esomeprazole, it says it has to be taken an hour
5 before a meal. That means there is a certain
6 hindrance for the absorption of solubility or for
7 the mechanism of action for the drug that has
8 clearly been captured. We do a lot of due
9 diligence on why that statement exists, and then go
10 back to the development and make sure that is
11 captured.

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

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

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

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

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

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

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

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

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

8 (No response.)

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

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

17 **Public Comment Period**

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

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

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

7 **Presentation - Jurgen Bulitta**

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

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

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

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

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

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

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

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

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

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

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

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

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

4 The model worked very well and was also
5 quite robust. The key parameters related to
6 pulmonary absorption are shown on this slide. The
7 first two lines show the absorption half-lives from
8 central and peripheral lung for the three
9 formulations, so A having the largest MMAD, and B
10 and C being very similar with an MMAD of 3.7 and
11 3.8.

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

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

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

6 The central to peripheral lung deposition
7 ratio was clearly different based on this
8 population PK modeling analysis for the large
9 formulation A compared to B and C, with ratios of
10 3.1 for A and around 1.0 for B and C.

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

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

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

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

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

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

18 What we observed for in the clinical trial
19 was that the peak concentration for formulation C
20 was 80 percent higher than that of formulation A,
21 clearly suggesting that there is sensitivity of
22 C_{max} to inform about the central to peripheral lung

1 deposition ratio.

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

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

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

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

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

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

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

1 them with different available mouth, throat models,
2 8 of those, and things like droplet size
3 distribution, APSDs, the plume geometry and
4 dissolution profiles would be recorded in an effort
5 to better understand what are the most realistic
6 and most informative testing conditions for these
7 metered-dose inhaler formulations to make decisions
8 for regulatory development and approval.

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

13 (Applause.)

14 DR. LIONBERGER: Thank you very much.

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

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

20 **Presentation - Priscilla Zawislak**

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

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

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

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

22 Our first proposal is for FDA to evaluate

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

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

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

1 must do to submit their ANDAs today.

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

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

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

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

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

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

1 the feasibility for the safety and toxicology of
2 these grades.

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

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

16 (Applause.)

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

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

1 challenges in implementing new analytical methods.

2 **Presentation - Darby Kozak**

3 DR. KOZAK: Thanks, Rob.

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

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

22 I'd like to present a couple of examples,

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

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

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

1 surface characterization.

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

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

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

22 Another complex active is actually the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 which ones do you see potential issues with.

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

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

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

22 DR. LIONBERGER: Thank you, Darby.

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

5 **Presentation - Liang Zhao**

6 DR. ZHAO: Thanks, Rob.

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

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

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

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

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

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

22 I just want to download here that our

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

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

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

1 and the model should be sufficiently verified.

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

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

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

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

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

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

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

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

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

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

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

1 point.

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

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

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

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

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

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

13 (Applause.)

14 **Panel Discussion**

15 DR. LIONBERGER: Thank you, Liang.

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

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

3 DR. LI: Yes --

4 DR. LIONBERGER: Who is your question for?

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

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

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

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

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

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

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

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

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

1 doing a full globalization.

2 Guenther, do you wish to comment?

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

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

1 information on regional deposition.

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

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

14 DR. LI: Thank you.

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

17 DR. BHOOPATHY: For Darby.

18 DR. LIONBERGER: Go ahead.

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

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

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

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

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

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

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

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

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

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

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

17 DR. BHOOPATHY: Thank you.

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

1 on the analytical and the quantitative sides.

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

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

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

1 particularly on the new analytical methods.

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

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

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

1 good?

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

9 DR. LIONBERGER: Jim, any comment?

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

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

22 Just in my own working environment, since

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

8 I'm just kind of curious. I will just ask
9 a question. I understand from Dr. Choe there was
10 90 pre-ANDA meetings or something like that. I
11 think one or two industrial colleagues have told me
12 don't ever tell the FDA anything that you're not
13 sure about. I'm just kind of wondering how some of
14 those things go.

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

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

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

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

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

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

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

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

22 Any time new things come, a lot more work

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

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

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

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

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

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

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

9 DR. LIONBERGER: Katherine?

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

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

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

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

6 DR. LIONBERGER: Guenther, and then Bing?

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

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

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

19 DR. LIONBERGER: Bing?

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

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

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

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

22 So the key question is, can you develop a

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

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

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

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

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

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

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

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

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

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

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

14 DR. LIONBERGER: Comments? Guenther?

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

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

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

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

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

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

1 impediment.

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

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

12 DR. LIONBERGER: Liang?

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

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

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

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

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

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

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(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 (1:03 p.m.)

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

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

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

17 **Presentation - Lei Zhang**

18 DR. ZHANG: Thank you, Rob.

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

22 As we all know, generic drugs in the United

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

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

14 Last year, following the public workshop,
15 we proposed the FY 2019 GDUFA research science
16 product areas, focused on 4 broad categories with
17 15 product areas, which I'm not going to go through
18 all of them, but we know, among the 4 broad
19 categories, 3 of them are very clearly associated
20 with the complex product categories. The fourth
21 category, we focus on the tools and methodologies
22 that would cover both complex products and

1 non-complex products.

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

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

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

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

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

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

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

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

22 As you are aware, GDUFA II started in

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 For fiscal year 2016, similarly, we see
2 5 out of 15 belong to the first broad category with
3 1 complex API, 1 long-acting injectable, 1
4 abuse-deterrence formulation; and 1 complex
5 injectable, and 7 out of 15 products belong to the
6 complex route of delivery with the common route we
7 saw as nasal inhalation, topical, and intrauterine.

8 Again, we also see 9 out of 15 comp
9 products, which is 60 percent of them belong to the
10 complex drug-device combination; 2 implanters;
11 3 auto-injectors; and 4 drug-delivered device
12 combination.

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

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

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

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

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

1 Now, we're going to focus on last fiscal
2 year 2018 NDA approval cohorts with regard to
3 complex products only. So we have a total of
4 40 NDA-approved that are complex products. We have
5 already developed 6 PSGs, and 7 of those are new
6 molecular entity complex products. As of February,
7 we already have 1 PSG developed, which is a topical
8 product.

9 This table lists all the complex NME
10 approved in fiscal year 2018, so in total there are
11 7 of them. As I mentioned earlier, one of them, we
12 already have a PSG, and there's another 3 where
13 research conducted in previous years has prepared
14 us to develop PSG for those complex products, and
15 we plan to develop PSG for those products in the
16 next 12 months.

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

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

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

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

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

22 Also, another new drug-device product was

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

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

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

15 (Applause.)

16 DR. LIONBERGER: Thank you, Lei.

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

20 **Presentation - Jason Rodriguez**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 In the figure we show here is a study from
19 2015 where we're looking at glatiramer acetate and
20 its comparator, the RLD and the comparator product.
21 We use high-resolution LC-MS to show that the early
22 elution times, we're able to differentiate between

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

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

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

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

1 complex route of delivery.

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

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

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

1 complex formulations.

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

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

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

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

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

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

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

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

1 hours that are devoted to trying to get answers.

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

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

1 the areas where we will hope to continue working
2 together.

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

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

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

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

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

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

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

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

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

7 (Applause.)

8 **Public Comment Period**

9 DR. LIONBERGER: Thank you, Jason.

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

14 **Presentation - Vinod Shah**

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

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

1 ensure patient safety and the benefit.

2 (Pause.)

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

5 (Laughter.)

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

9 (Laughter.)

10 DR. SHAH: Thank you, Mehul.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 I finished in time in spite of all the

1 complex difficulties.

2 (Applause.)

3 **Panel Discussion**

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

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

10 DR. GOBBURU: Joga Gobburu, University of
11 Maryland.

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

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

20 DR. POLLI: James Polli, University of
21 Maryland.

22 DR. STIER: Ethan Stier, acting deputy

1 office director, Office of Bioequivalence.

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

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

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

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

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

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

22 DR. SHAH: There is a great similarity

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

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

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

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

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

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

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

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

1 products which have been approved.

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

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

14 DR. LIONBERGER: Let's move on.

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

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

22 DR. RODRIGUEZ: I can go ahead and start if

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

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

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

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

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

10 DR. LIONBERGER: Bob?

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

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

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

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

1 about.

2 DR. LIONBERGER: Right.

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

9 They all have to do studies. The study may
10 be the clinical outcome or it may not be, but it's
11 some pharmacologic effect. It's a little tricky
12 because you have to do it somewhere steep, a steep
13 part of the dose-response curve, or you'll miss
14 important differences.

15 But is that what we're talking about, that
16 you have to do a study that show that something
17 happens?

18 DR. LIONBERGER: The standard for approval
19 for generic products for bioequivalence, as you can
20 imagine, is that we have enough evidence that the
21 drug delivery to the site of action is the same.
22 We can do that by blood levels. We sometimes do

1 that through looking at clinical data. But we also
2 do it through looking at the in vitro performance
3 of the product, and the drug delivery rate, and the
4 comparison between the two products.

5 So a lot of the laboratory work and science
6 on these more complex products is saying what's the
7 delivery rate or the release mechanism from those
8 products, and can it be measured correctly and
9 accurately in the laboratory characterizations? So
10 the in vitro approach is on the table as well.

11 DR. TEMPLE: You always have to wonder
12 whether the in vitro method figures out how the
13 lung works.

14 DR. LIONBERGER: Right, and that's why
15 we're doing research in these different areas.

16 Jason, can you comment a little bit on, in
17 Lei's presentation, she identified some new types
18 of API that we really haven't seen before, so I'm
19 thinking of the oligonucleotides and the anti-sense
20 RNA.

21 Can you talk a little bit about OTRs,
22 experience in characterizing those, and how well

1 characterized do you think are the NDAs, how pure
2 are they, what kind of analytical methods has the
3 lab developed or is developing for those types of
4 new APIs that really haven't been seen in
5 CDER-approved products until very recently?

6 DR. RODRIGUEZ: Right. I think that one of
7 the areas that OTR is working on under the broad
8 umbrella of oligonucleotides is developing a
9 research program where we have stakeholders from
10 several different areas of CDER, including OGD.

11 One of the areas and considerations, when
12 we're looking at some of these complex APIs and
13 complex drugs, is that there is a different point
14 of view based on the office that you're from. When
15 you're thinking about the laboratory studies, it's
16 very important to capture and cast a broad net out
17 to get those points of views.

18 From a laboratory perspective, once we
19 harness what is the considerations from each
20 stakeholder, then it's important for us to develop
21 what is the path forward in the laboratory.

22 So I see, in a lot of these areas, the path

1 forward includes a combination of maybe advanced
2 chromatography and also high-resolution mass spec
3 work. That is one of the areas where we made a lot
4 of investments in the laboratory to try to stay up
5 to what's currently available. So that's one of
6 the areas from a logistical point of view.

7 Now, when we look at these from the new
8 drug arena, for example, and some of these do come
9 to us from the method verification program, one of
10 the things that we do look at is we do have
11 discussions with the review staff of what are the
12 areas that you are considering? We don't take
13 these consults and just look at anything. We
14 always are looking at a targeted area that the
15 review divisions have asked us to focus on.

16 So that's an important piece of knowledge.
17 It's in the knowledge bank of what are the areas
18 that are being considered now, that we use then
19 when we're developing these longer, I would say,
20 three- to five-year research programs on how we
21 developed the path forward. I hope that, in a
22 roundabout way, answers the question there.

1 DR. LIONBERGER: Katherine, do you have
2 comments?

3 DR. TYNER: I would just follow up and give
4 a signal-boost, that the labs really are well
5 equipped. One of the things that we try to get
6 from the public input is what instrumentation that
7 we need to be making sure that we have available
8 and that we have knowledge of.

9 DR. LIONBERGER: Joga, and then Markham?

10 DR. GOBBURU: Just to be clear, the
11 drug-device combination, the specific question is
12 more about the really long, shall we say, acting --

13 DR. LIONBERGER: I think one category of
14 products that we saw in this list was a very
15 long-acting injectable. So these are implanted for
16 up to 3 months at a time.

17 DR. GOBBURU: Yes. I can give you an
18 example. Actually, from my experience, the longer
19 the duration of release, the likelihood of
20 establishing an IRVC is much greater because you
21 are making at least the most rate-limiting step.

22 I have experience with IUD device, which is

1 for 5 years, and there is a very simple linear IRVC
2 showing -- yet, the device can be changed, but I'm
3 sure that the device comparison is pretty well
4 established of what type of physical and chemical
5 engineering characteristics comparison. But the
6 coating and then the release, there are methods to
7 accelerate and compare in vitro. We don't even
8 need in vivo studies.

9 DR. LIONBERGER: Markham?

10 DR. LUKE: I just want to point out the
11 beautiful juxtaposition of the two speakers and the
12 topics that they talked about. Lei talked about
13 the technological advances in new drugs, so each
14 new drug, especially the complex products, present
15 new technologies.

16 We're all for innovation and bringing new
17 products to our American patient population so they
18 can have good healthcare. But at the same time, in
19 keeping up, we have new technologies for getting at
20 microanalysis, getting at better and better
21 adjudication of small levels of drugs, looking at
22 incremental changes in drug concentration; for

1 example, doing subdermal concentrations of drugs
2 with really tiny samples, and better than Theranos
3 types of stuff.

4 So we're advancing technology to try to
5 keep up with the innovation in new drug
6 formulations and new drug products.

7 DR. LIONBERGER: Bob, do you have a
8 comment?

9 DR. TEMPLE: I just wanted to ask you about
10 your previous example. If you have a long-term
11 drug that releases slowly, you still can rely on
12 blood levels over time.

13 DR. LIONBERGER: So in that one, one of the
14 approaches is to do blood level studies. One of
15 the challenges that I think the generic industry
16 would say is that those studies are generally
17 not -- you generally can't do them in healthy
18 subjects, so they have to recruit patients on those
19 products for many of them, especially the long
20 exposure times.

21 So that could be a barrier to recruiting
22 the patients. Sometimes, when we have the

1 patients, you can't do the simple 1-dose crossover
2 study. You have to sort of switch the patients
3 during their treatment.

4 From the pharmacokinetic point of view, if
5 you have a 3-month dosing interval and you want to
6 switch them and let the new product come to steady
7 state, sometimes you have to have a multi-year
8 study. That's why I think, as Joga mentioned --

9 DR. TEMPLE: Especially if it's a 5-year --

10 DR. LIONBERGER: -- right, right -- that
11 when there are in vitro/in vivo correlations that
12 are used and sometimes been established, you know
13 that they're possible from work that the new drug
14 development has done, that that's an approach
15 toward a bioequivalence method.

16 Often, those are the focus of our research
17 activities to help develop the appropriate IV-IVC
18 type methods.

19 DR. TEMPLE: I guess my initial response is
20 the biggest problems where you don't really know
21 what the relationship with the blood level is to
22 what it does. One of the drugs that was listed

1 before was eteplirsen, where the approval was based
2 on an array of increases in dystrophin in the
3 muscle.

4 We have no idea what the relationship of
5 the blood levels to that was because the response
6 was hugely variable. I just wondered if people had
7 thoughts about how they were going to do that.

8 DR. LIONBERGER: I think that's an
9 injectable product. Right?

10 DR. TEMPLE: Yes.

11 DR. LIONBERGER: I think there's not a
12 bioavailability question there. There the issue
13 for the generic drug would be the same active
14 ingredient and --

15 DR. TEMPLE: But it's a fairly complex
16 molecule.

17 DR. LIONBERGER: Yes. And that's why the
18 analytical methods have to be developed to
19 characterize those more complex molecules.

20 DR. TEMPLE: But you think, maybe even if
21 it's a complex molecule, blood levels might do the
22 job?

1 DR. LIONBERGER: Yes, or again, generally
2 for injectable solutions, we generally don't think
3 we even have to because the bioavailability is
4 going to be 100 percent of its direct injection or
5 IV dosing.

6 Any other comments from the panel? Lei?

7 DR. ZHANG: Yes. I just want to go back to
8 that drug-device combination. When we think about
9 it, it's very complex because you have drug-device
10 interface, which we have a lot of research on, but
11 there's also user device interface, which I feel we
12 probably still struggle a little bit, especially it
13 depends on the design of the device and how a
14 patient is going to interact with the device, and
15 how we do appropriate comparison.

16 So I just wonder whether other
17 panelists --

18 DR. LIONBERGER: I think Lei's question was
19 about the human interactions with the drug-device
20 combination, so the user interface or human factors
21 question.

22 DR. GOBBURU: But I mean, for the device,

1 is it not a requirement for the device to be
2 approved in the first place? I thought we'd have
3 to do that.

4 DR. LIONBERGER: For the new drug device or
5 for the generic?

6 DR. GOBBURU: Yes, new drugs.

7 DR. LIONBERGER: I mean, the new drug
8 device has to be --

9 DR. GOBBURU: No, but the device for the
10 generics is usually the device that is approved.

11 DR. LIONBERGER: No.

12 DR. GOBBURU: Not necessarily?

13 DR. LIONBERGER: No.

14 DR. ZHANG: They can have it different.

15 DR. LUKE: So there's variability in how
16 combination products are approved. The combination
17 product is defined as a drug and a device used in
18 juxtaposition. The device may be part of the drug
19 application itself, so you can actually have a
20 device that's part of the NDA or you can have a
21 device as part of a PMA or 52K that's reviewed
22 separately by our sister center. But how those

1 products are used together is something that we
2 look at.

3 DR. LIONBERGER: For example, like the
4 inhalation devices, that's a device. It's a drug
5 delivery device. It doesn't have to be identical
6 in the generic versus the brand product. The
7 scientific question is what are the characteristics
8 between those two devices that have to be the same
9 in order for it to be a substitutable generic
10 product.

11 As Lei said in the first case, one aspect
12 is the drug delivery rates, which are more or less
13 measurable. You can measure them through the PK
14 effects. You can measure them through the in vitro
15 performance.

16 The other aspect of that comparison is how
17 the user uses the device. What actions does the
18 user have to take, and at what point do those
19 potential differences become so large that the
20 product you would not say are substitutable, and
21 what differences are still differences but still
22 allowed and wouldn't affect or impact substitutes?

1 That's the review question, and the OGD
2 review staff has to deal with all these combination
3 products, is if there is a difference in the
4 interface that the user has presented, is that
5 difference significant or not?

6 DR. GOBBURU: But to me, we already have
7 policies for that. Right? You compared the
8 within-subject variabilities. And if there is a
9 product within subject variability interaction, and
10 it goes, what is it, 2.5 or something like that,
11 there's a problem. So we can apply the same routes.

12 DR. LIONBERGER: If you think that your
13 drug delivery is the measure of successful use of
14 the device, I think that's --

15 DR. GOBBURU: But the clinical trial will
16 tell me both of them.

17 DR. VAITHIYALINGAM: It's not the question
18 of clinical trial or equivalency. For the device
19 differences between innovator product and generic
20 product, it shouldn't cause any confusion to follow
21 the labeling instructions in the original innovator
22 product.

1 DR. LIONBERGER: In the bioequivalence
2 studies, they're usually done under controlled
3 conditions where you ensure that the person uses
4 the device correctly. So you compare drug delivery
5 between two cases where both devices are used
6 correctly.

7 The user interface question, why it's more
8 difficult, is if you're not instructing patients
9 and they're just substituted, will they use it
10 correctly? And that's a very hard question to
11 answer.

12 DR. VAITHIYALINGAM: Both the devices have
13 to have the same instruction of use. If the
14 generic product has a different instruction of use,
15 then it is -- it won't be approved in the first
16 place.

17 DR. LIONBERGER: So maybe, Siva, you can
18 talk about, in the generic industry, when you're
19 developing these products, what are some of the
20 challenges in matching the device?

21 If anyone from the industry wants to
22 comment about that aspect of generic product

1 development, what are the specific challenges that
2 you see as product developers in this area of
3 products that have devices? And if you're not
4 willing to comment here, I encourage you to make
5 those comments to the docket.

6 MS. NEWCOMB: Hi. I'm Claire Newcomb from
7 Mylan. I would like to encourage you to stick
8 around to the next presentation because my
9 colleague and I from Teva and Mylan are going to
10 present on exactly this.

11 DR. LIONBERGER: So we may in the next
12 panel be able to come back to this a little bit
13 more. So Jim?

14 DR. POLLI: I'm an academic, so I don't
15 develop generic products for a living, but just
16 have some thoughts about my daily life. I'd like
17 the initiative to have good instrumentation because
18 it makes all the difference.

19 When I think about at least the time I
20 spent, I probably spent at least about 10 percent
21 of my time just trying to stay up with analytical
22 methodology. I think we spent a lot more time than

1 we might think, and that's very important over the
2 long haul. Maybe my major point.

3 DR. LIONBERGER: So Mehul?

4 DR. MEHTA: Just the general thoughts about
5 Lei's presentation and then OGD, this mandated
6 requirement of PSGs, especially for complex drugs.
7 I think the OGD is focusing the effort in the right
8 direction, and now we are collaborating even more
9 and more on our new drugs and generics, or
10 identifying these complex products.

11 The questions that you were asking are,
12 these are all questions that are important
13 questions that need to be paid attention to at the
14 approval time, the new drug approval time.

15 DR. LIONBERGER: I think some of those
16 also come up in the new drug to review as companies
17 make changes during their development process that
18 you and especially probably the Office of Clinical
19 Pharmacology see and have to bridge through the
20 development process.

21 DR. MEHTA: That sharing of information,
22 knowledge, across our organizations, I think, is

1 getting better and better. I think, especially
2 with the PSGs, that you have [indiscernible]. I
3 just see that as a lot of good collaboration.

4 DR. LIONBERGER: I believe that we will
5 have a break, and then we will reset for our final
6 panel of the day. So we'll be back in 15 minutes.

7 (Whereupon, at 2:10 p.m., a recess was
8 taken.)

9 DR. LUKE: Hello. Welcome back. Welcome
10 to the afternoon session for the Generic Drug
11 Workshop 2019. We have a speaker who exemplifies
12 that good generic science does not know national
13 boundaries.

14 Walter Wigger-Alberti is a CEO and clinical
15 advisor for dermatology for Bioskin GmbH, and he's
16 going to be speaking about specific challenges in
17 the evaluation of irritation and sensitization for
18 transdermal systems, a dermatological appraisal
19 focusing on scoring and application. Walter?

20 **Presentation - Walter Wigger-Alberti**

21 DR. WIGGER-ALBERTI: Hello, and good
22 afternoon to everybody in the room who I

1 unfortunately cannot see. I strongly apologize
2 that I was not able to come in person, but I truly
3 believe that this has a great value for the
4 equibalance. I would like to thank Steven for the
5 technical assistance.

6 The purpose of my presentation is to
7 highlight the challenges for the current
8 recommendations by the FDA for the application
9 procedure and scoring in phase 1 studies with
10 transdermals.

11 We all know that transdermals may cause
12 irritant reactions due to their occlusive
13 application of adhesive materials and sometimes
14 even cause allergic reactions. So that is why they
15 should be applied once daily on intact skin only.
16 The application side is to be rotated daily. And
17 any application should not be used more than once
18 in 14 days. This is for patients and not intended
19 to apply them repeatedly on the same skin area.

20 However, cumulative irritation is usually
21 tested with repeated applications on the same skin
22 area for topical drugs such as creams and

1 ointments, also under occlusion using test
2 chambers. The reason is that we want to maximize
3 skin response to early detect and to compare
4 irritant potential of drugs.

5 A 5-day test design is only sometimes used
6 before authorities may allow goal or no-goal
7 decisions and to go into patient. But the
8 classical phase 1 trial as part of the
9 [indiscernible], however, is 21-day cumulative
10 application with daily application or sometimes
11 only 15 applications over 21 days, where the
12 products stay on the skin over the weekend.

13 For the testing of the sensitization
14 potential, we start usually with an induction
15 phase, also over 21 days, but with only
16 9 applications in total because the test products
17 stay on the skin for 48 or 72 hours. And after
18 [indiscernible] for usually 2 weeks, the products
19 are to be applied on a new test area once and the
20 readings are performed over 48 or 72 and sometimes
21 96 hours.

22 During the challenge phase, it has to be

1 decided by the investigators if the reactions are
2 likely to be irritant or allergic. Typical
3 examples for irritation can be seen above with low
4 levels of scoring and/or decrease of test reactions
5 such as 2, 1, 1, 0.

6 Allergic reactions are usually stronger,
7 stay longer, and they also increase [indiscernible]
8 evaluation even though the product was applied only
9 once. For example, as you see below, a score was 1
10 and then followed by score 2, 2, and even a 3.

11 Here, you can see a typical mild irritant
12 reaction to a transdermal. It's a sharply marked
13 erythema, some follicular spotty erythema. This is
14 really a mild reaction. But on the next picture,
15 you hopefully see the additional infiltrate and
16 even some papules assigned for allergic reaction.

17 On the next picture, which is the next
18 reading of the same lesion, you see even stronger,
19 and on the last picture, on the last reading, you
20 even see the edema is now crossing the
21 [indiscernible], spreading over the area the patch
22 was applied. So these are clear signs of an

1 allergic reaction to a transdermal.

2 Now we come to the problems with the
3 current scoring. So far, the standard for the
4 testing is given by the FDA guidance for industry,
5 for skin irritation, and sensitization testing of
6 generic transdermals. This has also been used as a
7 reference for other topical drugs. Ointments and
8 creams are tested almost the same way, and even the
9 latest EMA guideline refers partially to that FDA
10 guidance.

11 Now we are coming to the scoring system
12 that is presented in that guidance. It's claimed
13 to be a recommendation, but only a few companies
14 are brave enough to use other scores even though,
15 which I would like to explain, it is absolutely
16 inadequate for topical drugs in general and for
17 transdermal and special.

18 For any irritant reaction, the leading
19 symptom is erythema, and the erythema increases
20 with stronger irritant potential of the product to
21 be tested. But the score here presented is not
22 reflecting that. You may see that that's the score

1 with 1, which means minimal erythema, so that's now
2 a little increase with the two definite erythema,
3 but then it stays with erythema, and there are
4 papules with a score of 3 or 5, edema and papules;
5 6 is just vesicular eruption, and 4 is only edema.
6 There is no irritant reaction that increases, which
7 will reflect a score from 1 to 7, absolutely
8 impossible.

9 It's accompanied by another score which has
10 caused other impacts, and the other impacts are
11 focusing on symptoms as a result of dryness like
12 scaling, cracking, peeling, and so on. But this is
13 actually not seen in the application of
14 transdermals, and I will explain to you why.

15 I actually was wondering where the score
16 comes from and the Berger Bowman score that was
17 published in 1982 for testing the irritant
18 potential of cosmetic products, 150 cosmetic
19 products, they wanted to compare 14 days'
20 application with 21 days of application, but they
21 suggested that 14 days are enough to discriminate
22 topical products. However, this was news for

1 cosmetics, and they also themselves referred to an
2 older publication that you could see on the next
3 slide.

4 This publication from Lanman from 1968 in
5 which also cosmetics were tested, but particularly
6 bath oils and deodorants, products that have a high
7 level of detergent that of course may irritate and
8 they dry out the skin for which the other effect
9 scores might be useful, but not for transdermals.

10 But who decided that this is an adequate
11 score for topical drugs, and especially for
12 transdermals, where each removal of the plaster
13 itself removed also parts of the [indiscernible],
14 corneum and causes any signs despite the other
15 effect scores. So what we may see with the score
16 can't be seen because the transdermal is removing
17 it.

18 DR. LUKE: Walter, we have about 3 more
19 minutes for your presentation.

20 DR. WIGGER-ALBERTI: That's very short.
21 Okay.

22 (Laughter.)

1 DR. WIGGER-ALBERTI: On the next slide, we
2 see the typical increase of erythema as the leading
3 symptom of irritation. Next slide, this is just to
4 show that with the patch testing, the erythema
5 decreases. Edema is actually following the same,
6 and scaling is increasing, but this is after
7 removal of the patches over time. So it's totally
8 different information and it's only typical for
9 detergent. Sometimes, you get a positive control.

10 I would strongly recommend to use
11 alternative scoring such as the score presented
12 here, which is now also accepted as the score on
13 the question and answer paper by the EMA. Another
14 option is on the next slide. All these scores
15 reflect the leading symptom of erythema that
16 increases with higher rate and potential.

17 Now, we are coming to sensitization, where
18 for the induction phase, we should also use the
19 score with the leading symptom of erythema
20 increasing, and on the next slide, for the
21 challenge phase of the sensitization, we need
22 something that, of course, is assessing the

1 erythema, but much more the typical signs of
2 allergy, infiltration, papules, vesicles, and so
3 on.

4 It is not possible for me, due to the
5 shortage of time, to add another slide with a
6 recent publication from this year from the
7 Switzerland group, but they were using
8 [indiscernible] as an additional tool to assess and
9 measure irritant and allergic reactions, and they
10 were able to show that irritant reactions caused an
11 increase of temperature, but the increase of
12 temperature by allergic reactions are much more
13 higher.

14 So they were able to discriminate between
15 irritant allergic reactions, and this was confirmed
16 by an independent investigator who usually reads
17 test reactions; so very impressive, and I think
18 this is something where the discussion should be
19 open.

20 I hope I have some more minutes for the
21 application. You see that tape stripping using
22 test chambers may cause strong irritant reactions.

1 On the back, you see the typical back a person
2 where there were repeated applications of test
3 testers. Whenever we renew for test testers, and
4 this is the same as transdermals, we remove part of
5 the stratum corneum, which will disrupt the skin
6 barrier and may cause a lower level to induce
7 allergic reaction or allergies.

8 On the next slide is publication
9 demonstrating that tape stripping will increase
10 irritant reactions. We can skip this, and the next
11 slide is demonstrating the same for allergic
12 reactions, and we can also skip.

13 We now are at the slide with an example of
14 the rotigotine patch test. You see the results of
15 the sensitization during the challenge phase.
16 After 9 applications over 3 weeks in the induction
17 phase, there were only minor skin reactions seen in
18 the challenge phase, indicating that there is
19 actually no higher potential of sensitization.

20 But the same product, next slide -- and I'm
21 coming to the end -- was tested in the typical
22 21-day cumulative patch test, and here, you can see

1 that we have very strong reactions of the
2 rotigotine patch close to the positive control. I
3 can just say that many, many volunteers have to be
4 discontinued with the application.

5 If you would have seen the reactions, you
6 would have seen that these reactions have some
7 symptoms of allergic reactions. I'm sure we would
8 have seen positive test reactions if a challenge
9 phase would have been added. For me, this is the
10 reason why the 21-day approach with daily removal
11 of transdermal should be re-discussed.

12 I'm coming to my final slide, the
13 conclusion. The recommended score of the guidance
14 and the application you see is not adequate for
15 transdermal. The score has been developed for
16 topical formulations, in fact, cosmetics.

17 The leading symptom for irritation is
18 increasing erythema, and for allergic reactions,
19 additional symptoms such as papules and edema are
20 necessary, and the scores to be used should reflect
21 this development.

22 Finally, the 21-day daily application of

1 transdermals may cause all positive reactions and
2 even includes a higher risk for iatrogenic
3 sensitization, and I thank you for your attention.

4 (Applause.)

5 DR. LUKE: Thank you, Walter.

6 We're going to switch out the podium. I'm
7 going to introduce the next speaker from here. Our
8 next speaker will be Lisa Nilsson. Lisa is
9 associate director for the device RMB team at Teva,
10 and she is going to speak about challenges faced in
11 the development of the user interface for generic
12 and biosimilar combination products.

13 All yours, Lisa.

14 **Presentation - Lisa Nilsson**

15 MS. NILSSON: Thank you very much.

16 I'm going to talk about the challenges
17 faced in the development of the user interface for
18 generic and biosimilar combination products. I'm
19 going to focus on the device part and how the user,
20 which could be a patient, or a nurse, or a doctor
21 interacts with this device. In this case, the drug
22 is less important, even though, of course, the drug

1 will have impacts on how people deal with the
2 device.

3 In January 2017, there was a guidance
4 released from the FDA about how to do comparative
5 analysis and related comparative use, human factor
6 studies for drug-device combination products
7 submitted in ANDA. What this gave us was actually
8 some guidance of how to do the whole usability and
9 human factors process for generic devices. Before
10 that, we had more or less followed the same process
11 that we followed for our specialty product and
12 tried to tweak it through the generics. But you're
13 going to see that a very different approach is
14 taken.

15 This guidance was released, and we're very
16 grateful for this guidance. It was great to have
17 it. It actually gives very useful and practical
18 support on the development of generics, and it
19 clarifies that the generic combination product is
20 to be substituted without additional healthcare
21 professional interventional training. So it's
22 actually not that you have to be able to use all

1 the labeling per se.

2 It introduces three different types of
3 threshold analyses and how to categorize the
4 outcomes of them, and these threshold analyses are
5 looking into labeling, comparative tasks, and on
6 the fiscal aspects of the device.

7 They also have a chapter on the comparative
8 use human factors study. So this is a study that
9 would be intended to confirm the differences in
10 labeling a device can be substituted with the same
11 clinical effect and safety profile.

12 For a specialty product, there are also
13 human factors studies, cold semi-table validation
14 studies, but the purpose of them is to demonstrate
15 safety and effectiveness, so it's a different type
16 of study.

17 What do we do today? The typical process
18 for human factors in the industry would be to
19 follow this list, that first, you planned
20 activities, you identify users, use the use
21 environment operating principle. You identify and
22 capture use and needs, describe how the product is

1 used, review any known use issues, complete the
2 comparative analysis, would be labeling, task,
3 physical; look into the use-related risk
4 assessments, might do a comparative use human
5 factors study, and then complete the documentation.

6 The first four steps are very similar to
7 what we do for the specialty products. I think
8 that most people in the industry would say, "We got
9 this. We know how to do this." These four steps
10 are still a big challenge for most of the industry
11 and things that we discuss, all the things.

12 The first challenge we have is when we do
13 review of known use issues. We have a generic
14 device that we are developing, and we have the RLD.
15 So we would then do different searches on the RLD
16 and see what known issues there are.

17 The challenge we find here is, if the known
18 use issues review shows that there are existing
19 risks that originate the design or similar products
20 that were on the market, how can we control those
21 risks? Would this motivate minor design
22 differences driven by risk control or do we have to

1 do an exact copy even though we know that tiny,
2 tiny tweaks could make our device safer?

3 So this is something that we would like to
4 have a discussion with the FDA on what this space
5 is to do, looking at it from a risk perspective.

6 The next topic would be comparative
7 analysis. This is when we compare the originated
8 design with our proposed design in labeling, in the
9 use of tasks, and in the physical appearance of it.
10 We have to learn to examine all the external
11 critical design attributes of the proposed delivery
12 device constituent part in comparison to the
13 external critical design attributes of the RLD.

14 When we do this comparison, we can come up
15 with there's no difference. There might be a minor
16 difference and there might be another difference.
17 The problem here is when does a difference need to
18 be confirmed in a comparative use human factors
19 study and when another risk assessment is
20 acceptable?

21 Even though the guidance tells us that, if
22 you have no difference, it's likely not necessary

1 to do any other things. If you have minor
2 differences and it doesn't affect your external
3 critical design attributes, it will be likely
4 acceptable if you have some data or information to
5 support it. And if you have another difference,
6 you should first modify the design, but we know
7 that a lot of times, we cannot modify the design.
8 At that point, they might request additional data
9 or a human factors study.

10 The problem here for us is we know that
11 some of these differences might drive -- even
12 though we would put them through a human factors
13 study, a human factors study is a simulated use
14 study, so it's in a lab setting or similar.

15 We would only catch intentional use and the
16 type of foreseeable misuse that will spontaneously
17 come up in that study. In a lot of projects, we
18 know that there are foreseeable misuse scenarios
19 where we think that there might or might not be a
20 difference, but we can actually not test them
21 because some of these differences will only come up
22 in misuse, for example, and how can we then make

1 sure that this is covered in risk assessments, and
2 would actually other risk assessments be more
3 suitable than a human factors study in this case?

4 The next step is the risk assessment
5 itself. We followed design control, which means
6 that we need to show that risk control and
7 validation of user needs are done. A challenge for
8 the industry now is, if we do a comparative
9 analysis and we find the number of differences, how
10 can we demonstrate in a satisfactory way that we
11 have incorporated all of them in our risk
12 assessments?

13 Do we need to follow a completely different
14 process for risk assessments when it comes to
15 generics or should we follow the usual process that
16 we follow for specialty products, and then just add
17 any comparative risks we find?

18 We would really like if FDA could share
19 with us examples of what they have seen so far or
20 tell us that we've seen people doing this that
21 worked well, or we've seen people doing this and
22 that didn't work well because this is a source of

1 endless discussions within device development, and
2 the main goal is to make sure that our devices are
3 completely safe and that we can prove it.

4 When it comes to the comparative use human
5 factors study, we've decided we need to do one of
6 those. Our big struggle here is how do we plan it.
7 Human factors has always been a qualitative
8 science, and in this new guidance, they talk about
9 the comparative use human factors study as a
10 noninferiority study. Suddenly, we moved from a
11 qualitative science to a quantitative science, so
12 we need a lot of things to be able to calculate the
13 sample size. We need to have the acceptable
14 deviance above the error rate. Should that be
15 10 percent or is it something else?

16 We need assumed error rates, but we don't
17 know them until we run a study, so we then need to
18 run a study just to calculate error rates to
19 running a proper study and also which study power
20 is required.

21 So when it comes to specialty, we get a lot
22 of guidance on sample sizes. We would really like

1 more guidance from the FDA in this case on how
2 large do our sample sizes for a comparative use
3 human factors study need to be?

4 When it comes to challenges in the
5 development of instructions, sometimes the IP is
6 restricted, so we cannot have exactly the same
7 device, for example, so our device will look
8 different and have minor differences in aesthetics.
9 How can we do that with the instructions?

10 Also, the IFUs are often outdated. We
11 might copy a device that is 20 years old, so
12 instructions for use nowadays might look completely
13 different. We might have a different environment
14 that we work in so people interpret things
15 differently. What differences would be acceptable
16 to make it more safe and effective for the user?

17 I have some examples of IFU design, so
18 things that we would like to look into in
19 information flow, device presentation, images,
20 warnings. If all the warnings are at the end,
21 maybe it would be better to have them mixed up in
22 the instructions so we know that people actually

1 will read them.

2 Continuity and text; we also have an
3 example of the information flow. In this example,
4 the instructions tell you to unscrew the needle and
5 throw it away together with a pen. And then, in a
6 step later on, it tells you that you can also now
7 put the cap back on your pen and keep it for the
8 next use. We would like to rephrase this slide,
9 please, so people don't discard a pen when they
10 still have 27 doses in the pen. Can we do that or
11 do we have to stick to exactly what the RLD has
12 written?

13 There might also be examples in the IFU
14 where we have images that might not be as clear as
15 they could be, labels that they are. There might
16 not be a picture of the device in the beginning of
17 the IFU, something that I've seen that's a very
18 good thing to do to orientate the user towards the
19 device. For example, one device has a picture
20 showing a person spitting. Do we need to include
21 that? People know how to spit. We could focus the
22 space we have on something more useful.

1 I want to say thank you to my colleague,
2 Claire at Mylan for doing this. Thank you very
3 much.

4 (Applause.)

5 DR. LUKE: Thank you, Lisa.

6 Our next speaker; we have Joga Gobburu,
7 professor of pharmacy practice and science from the
8 University of Maryland. He's going to be speaking
9 on a potential role for innovative Bayesian and
10 PBPK approaches to generic drug development.

11 **Presentation - Joga Gobburu**

12 DR. GOBBURU: Thank you very much for the
13 opportunity. I really had two major points to
14 make. The following is the background. Currently,
15 there are certain products for which an efficacy
16 study is required and to support generic approval.
17 For these products, drug exposures cannot be
18 measured or systemic levels deemed not to be
19 relevant to the [indiscernible] or the local
20 variability.

21 Several such products do not have generics,
22 so if you go to the list of products on the FDA

1 website, you will find these. There is a serious
2 need in terms of, from a patient's point of view,
3 the cost. The agency, I think, is generally
4 interested in solving that problem.

5 Some of the challenges are along these
6 lines; one, the inability to distinguish between
7 placebo. On top of that, then you also have to do
8 noninferiority to the brand, and then of course,
9 the patients. It's not that there are no companies
10 who are attempting to do these, but most of them
11 failed. That is the problem I'm trying to address.

12 It is generally accepted that drug levels
13 are more sensitive than clinical endpoints. I
14 don't think I need to convince this audience about
15 that. But how do we potentially overcome this
16 challenge of a clinical trial hurdle? Let's
17 consider two cases: one, systemic levels cannot be
18 measured. So this is a locally administered
19 product and systemic levels cannot be measured.

20 The other is systemic levels can be
21 measured, but because the law says it should be the
22 rate and extent of bioavailability of the site of

1 administration, it has to be reflective at the site
2 of administration, systemic levels are not used by
3 us right now.

4 Let's say that systemic levels cannot be
5 measured. The proposal I have is that, currently,
6 a frequentist approach is proposed, meaning you
7 would have to recruit patients, and then you use
8 the clinical endpoint, whatever it is. And then
9 you would have to show superiority over the
10 placebo, and probably you'd have to show
11 noninferiority of some kind of comparison with the
12 brand also.

13 So the fundamental challenge here is that
14 some of these medications, like for pain and so on,
15 local, is very challenging to distinguish from
16 placebo. Even for a new molecular entity, there
17 are so many failed trials for these kinds of
18 indications because the placebo is a moving target.
19 Depending on who you recruit, the placebo responses
20 are vastly different.

21 So in that case, then in the spirit of the
22 generic rule, which is to make these products

1 available to patients at affordable prices, then
2 there has to be some balance between that versus
3 the low probability of distinguishing from placebo
4 itself when we know that there is an active drug.

5 My proposal is we use Bayesian approach and
6 borrow the strength from the other trials. It
7 could be published trials or even the trials from
8 the summary bases of approval. Then use that
9 double delta, meaning we change from placebo and
10 baseline, as a strong prior because those are
11 registration trials. Those are like the holy grail
12 for the approval of the drug. So there is no
13 ambiguity, uncertainty. It is not like an opinion
14 that you are asking somebody. It is reviewed by
15 the FDA. It is within the files of the FDA, so the
16 certainty of the prior information is very strong.

17 So I know that with great certainty I can
18 use that as an informative prior to help both
19 alleviate or bolster a little bit of support the
20 differentiation from placebo, as well as in cutting
21 down the size of the study. So that is a specific
22 recommendation I have for us to consider.

1 Naturally, the Bayesian theory is not new, but
2 application in the realm of generic drugs is
3 something that we can seriously consider.

4 Now, what if systemic levels can be
5 measured? Now, here is a proposal. I will try, as
6 much as possible, to be very clear because it's a
7 very subtle proposal I'm making.

8 Let us say that, through this research, we
9 establish a PBPK model for a certain dermal
10 product, shall we say. Because it is a dermal
11 product, although you can measure the levels very
12 well systemically, we don't want to use it because
13 that's not reflective of the rate of absorption and
14 variability.

15 So because now we have a PBPK model
16 connecting the drug from its administration all the
17 way to the systemic circulation, I now know the
18 relationship between the local concentrations.
19 What happens before the local concentrations is
20 already taken care of. I'm not worried about that
21 now.

22 The correlation between the local

1 concentrations and the systemic is biologic. It
2 has nothing to do -- its meaning physiologic. It
3 has nothing to do with the product itself because
4 it is about the blood flow, the partitioning, and
5 availability between the local tissue and the
6 systemic circulations.

7 So I have to do that PBPK model only once.
8 Once I prove the correlation between the local
9 concentrations and the systemic, I throw the PBPK
10 model away. I don't need it. I will use the
11 systemic circulation just to do the bioequivalence,
12 and I'm done. Otherwise, it puts a lot of burden
13 on so many sponsors. Everybody has to do this PBPK
14 or somehow access it, but why repeat the same signs
15 over and over again? I already established the
16 relationship. I will just use systemic levels for
17 the bioequivalence.

18 This is a proposal where you have it
19 reasonable. It doesn't need to be highly evaluated
20 in my opinion for this purpose. It has to be a
21 reasonable PBPK model, and that's my second
22 proposal.

1 So that was it, and I yield almost
2 3 minutes back to the next speaker.

3 (Laughter.)

4 (Applause.)

5 DR. LUKE: Thank you, Joga, for yielding.

6 Our next speaker is Kiran Krishnan. He's
7 the senior vice president, global regulatory
8 affairs for Apotex. He's going to be speaking
9 about demonstrating the U.S. reference standard and
10 foreign reference standard sameness. Kiran?

11 **Presentation - Kiran Krishnan**

12 DR. KRISHNAN: Hi, Good evening. I'm here
13 to talk about a specific research request,
14 demonstrate sameness between the U.S. reference
15 standard and the foreign reference standard.

16 The agenda that I will be covering today is
17 specifically what is a research request, give you a
18 little bit about the global regulator's
19 perspective, some recommendations, and what are the
20 benefits of the request that we're making. And
21 finally, we'll close out.

22 Now, the specific research request is we're

1 requesting agency to conduct research to establish
2 a criteria that could be used as a basis to
3 demonstrate the sameness between the U.S. reference
4 product and the foreign reference product.

5 Just to give you a perspective of what
6 happens across the globe, what we found is there
7 are two global regulators; that is, Health Canada
8 and TGA that is in Australia. They both allow the
9 use of foreign reference standard, and there are
10 three general principles that they have considered.

11 One is the product is registered in a
12 country with a compatible regulatory system. It's
13 marketed in the country or origin by the same
14 innovator, company or corporate entity, which
15 markets the same product in their country. Of
16 course, they also have a criteria that it should
17 not be a narrow therapeutic index drug or require
18 careful patient monitoring. Those are the basic
19 underlying principles.

20 Now, there are actually published guidances
21 in these jurisdictions. Just to give you a high-
22 level overview of the Australian guidance or the

1 TGA guidance, it's much more broader compared to
2 Health Canada, but what TGA says to demonstrate
3 sameness is you need an assessment or comparison of
4 the labeling on the product information between the
5 reference product in Australia and the foreign
6 reference product.

7 They need the certificate of analysis for
8 both the reference product, comparative dissolution
9 profile in at least 3 media, same nominal quantity
10 of drug substance, same size, weight, and type of
11 coating, physical chemical evidence that the
12 products are quantitatively identical.

13 So as you can see here, it's a much
14 high-level overview focusing mainly on the solid
15 oral dosage form.

16 If you look at Health Canada, the guidance
17 from Health Canada on this topic has specific
18 requirements for dosage forms. If you look at
19 immediate-release, they talk about, again,
20 assessment and comparison of the labeling and
21 product information; C of A's of the reference
22 products; medicine ingredient is considered to have

1 high solubility and they are requiring that the
2 products have same color, shape, size, weight, type
3 of coating, and scoring conflagration; and the
4 non-medicine ingredients are qualitatively the
5 same; and of course, they're asking for comparative
6 dissolution profiles in 3 media.

7 They've also gone one level higher and
8 they're looking at demonstrating the sameness for
9 immediate-release orally inhaled dry powders.
10 Again, in that case, they're looking for assessment
11 of comparison of labeling, identical amount of
12 medicine ingredient, C of A's of both reference
13 products.

14 In terms of formulation, the expectation is
15 the non-medicine ingredients are qualitatively and
16 quantitatively the same within plus or minus 5
17 percent of each excipient. The physicochemical
18 properties and in vitro performance are essentially
19 the same, plus or minus 10 percent, and plus or
20 minus 10 percent. And again, they're looking at
21 device attributes. The device attributes, the
22 qualitative and quantitative analyses of physical

1 and operating characteristics of the devices are
2 same or similar.

3 Now, based on what we've seen with
4 Australia and Health Canada, what we are
5 recommending is the agency conduct research to
6 establish a criteria that could be used as a basis
7 to demonstrate sameness of the U.S. reference
8 product and the foreign reference product for the
9 following dosages, for soluble immediate-release,
10 could be extended to modified release, including
11 for complex products like products with complex
12 APIs, complex formulations, complex route
13 deliveries, and other complex dosage forms.

14 What are the benefits of this research?
15 One is around public safety. You don't want to be
16 doing the studies again and again for the same
17 product. You end up doing multiple studies for
18 different jurisdictions.

19 The other important part is timely
20 development and approval of generic drugs and
21 increased access to affordable medications. Now,
22 obviously, when you try to do one study, you cut

1 down on the timelines that is needed for
2 development.

3 One thing to also be noted is sometimes --
4 and the agency is very well aware of it -- it's
5 very difficult to source some of the innovative
6 products in the U.S., because obviously, they're in
7 restricted distribution. In those instances, we
8 find that products are more easily sourced in other
9 geographies by the same innovator products.

10 So that is a need that the agency
11 itself -- there's a big push from the agency to
12 find out ways and means of solving the problems.
13 We believe that this is one that could actually
14 indirectly solve that problem.

15 Also, it supports global development now,
16 and the agency has proposed -- actually, we want to
17 compliment the agency for its proposal to ICH,
18 where FDA submitted its reflection on further
19 opportunities for harmonization of standards in
20 generic drug development. This actually would
21 probably help in that direction.

22 In summary, what we were requesting is, in

1 order to improve patient access to high-quality
2 affordable generic drugs, this research outcome can
3 provide industry with guidance on how to
4 demonstrate sameness between the U.S. reference
5 standard and the foreign reference standard.

6 Ultimately, what we are hoping is this
7 research could enable a revision to the regulation
8 down the line, which could allow the use of foreign
9 reference standards for us to conduct
10 bioequivalence studies to support the generic drug
11 approval process in the U.S. Thank you.

12 (Applause.)

13 DR. LUKE: Thank you, Kiran.

14 Back to Rob?

15 **Public Comment Period**

16 DR. LIONBERGER: Yes. So now, we're moving
17 to our open public comment portion of the session,
18 so our first speaker in the session is Vatsala
19 Naageshwaran from Absorption Systems.

20 **Presentation - Vatsala Naageshwaran**

21 MS. NAAGESHWARAN: Thank you, FDA, for
22 giving me the opportunity to present at the forum.

1 Despite the presence of topical ophthalmics, there
2 is a lack of genetic substitutes for conventional
3 dosage forms like suspensions, ointment, and gels
4 that can be attributed to the barrier imposed by
5 the clinical endpoint in aqueous human PK studies
6 that are currently required for bioequivalence.

7 A recent publication from the Office of
8 Bioequivalence highlighted through a retrospective
9 analysis of aqueous human studies differences in
10 demographic data like gender, and race, and age,
11 which influence the outcomes, the bias that was
12 introduced because of the covariate
13 imbalance -- and clinical endpoint studies,
14 multiple speakers have spoken about the
15 insensitivity, and especially where there's disease
16 heterogeneity and demographic factors, you can have
17 results that don't match within identical trials.

18 ORS has supported a lot of research
19 initiatives to identify alternative approaches such
20 as Q3 characterization to demonstrate structural
21 similarity that can provide a fingerprint match of
22 the physical-chemical characterizations to confirm

1 in vivo performance, and they have translated this
2 into a subset of product as an option and a subset
3 of product guidances.

4 The principle of characterization-based
5 equivalence being the fact that pharmaceutical
6 equivalence, especially for ophthalmic products,
7 complex ophthalmics, doesn't always translate to
8 therapeutic equivalence since Q1/Q2 formulations
9 can have different physicochemical properties that
10 can impact the in vivo performance of the product.

11 IVRT, which has been used to requalify an
12 initially approved product following an acceptable
13 change, is also utilized as part of this Q3
14 approach primarily for manufacturing tolerance to
15 assure lack of process variability.

16 There are significant limitations with this
17 approach. Since outcomes from Q3 testing can be
18 influenced by methodologies, there is no
19 established criteria for comparability, and
20 importantly, neither Q3 nor IVRT have correlation
21 to critical in vivo parameters like precorneal
22 residence time and rate and extent of drug delivery

1 to the target site of action.

2 So illustrated in the slide are Q3
3 characterization data for a suspension product. We
4 were looking at two important CQAs that are
5 associated with topical ophthalmics, viscosity,
6 which is an important critical quality attribute
7 because it increases ocular bioavailability by
8 increasing residence time. But the specifications
9 for the polymers that are used for viscosification
10 can be very wide, and this results in a range of
11 viscosities that is obtained for different lots of
12 RLD.

13 Additionally, there are multiple
14 experimental factors that can also impact or
15 provide different outcomes. And similarly, with
16 looking at particle size, which is also an
17 important CQA for a topical ophthalmic, we see
18 several experimental factors that can bias the
19 results.

20 A key question remains as to what is
21 relevant. Is it the size of the native dispersed
22 or the actual aggregated particles that are within

1 the product?

2 The FDA is keenly aware of these
3 limitations. They have initiated efforts, as you
4 can see on this slide, to support new research in
5 multiple areas that include in vitro permeability
6 across corneal and conjunctive barriers, tissue
7 distribution, PK and PD models in nonclinical
8 models, and ocular PBPK and PK/PD model development
9 and refinement.

10 Absorption Systems has established and
11 validated in vitro and nonclinical models to
12 augment formulation characterization for close to
13 two decades for the advancement and market approval
14 of novel therapies for topical ophthalmics. We are
15 completely aligned with FDA's efforts to take an
16 integrated approach by incorporating functional
17 assets for confirmatory evidence of therapeutic
18 equivalence.

19 Complex ophthalmic products elicit
20 biological activity by multiple mechanisms, which
21 may not all be sequential. And in many instances,
22 they have layered biology with early through

1 extended mechanisms of action that are dependent on
2 formulation properties.

3 So when a drop of formulation is
4 administered to the ocular surface, it interacts
5 with the biomechanical barrier of the cornea before
6 it can actually penetrate through the ocular
7 surface. This interaction and permeation really
8 depends on the transformation of the formulation
9 that occurs on the ocular surface as well as the
10 dynamic conditions that are present there.

11 So how do we recapitulate formulation
12 biomorphology on the ocular surface given its
13 criticality in determining bioavailability and
14 efficacy?

15 Performance at the site of administration
16 can be evaluated by IVPT studies using excised
17 corneal and conjunctival tissue that can be
18 predictive of in vivo bioavailability. In vitro
19 studies using either rabbit or human cornea can
20 provide significant information with regard to the
21 rate of transfer, from the donor through the cornea
22 into the receiver chamber; so absorption and

1 desorption rates that can be estimated that enables
2 us to not only study the effect of various
3 formulation characteristics on the permeability of
4 drugs, but also to predict ocular kinetics in
5 human.

6 IVPT, however, doesn't factor the surface
7 dynamics at the site of administration, so
8 retention or loss of product from the ocular
9 surface. Rabbits are the preferred surrogates for
10 topical ocular drug PK and PD studies because their
11 eye anatomy and physiology resembles human, whether
12 that's geovolume [ph] turnover rate, pH, of the
13 tear fluid, or milliosmolarity of tears. It's very
14 comparable to humans.

15 So you can evaluate the thickness of the
16 tear film, for example, with optical tomography.
17 You can measure drug levels in tears, collected
18 using Schirmer tear strips. And these are all very
19 useful ways to perform or monitor comparative
20 surface dynamics between a reference and a test
21 formulation.

22 Primarily, most direct route of drug

1 penetration into the anterior chamber is the
2 cornea, but this is really only 20 percent of the
3 ocular surface, and it presents a very tight
4 lipophilic barrier.

5 A secondary route by which molecules can
6 reach intraocular tissue is the conjunctiva, which
7 has inverse properties to the cornea by being a
8 leaky barrier. But most formulations are typically
9 optimized to enable both ideal transcorneal and
10 transconjunctival transfer.

11 We don't know the absorption distribution
12 and elimination of ocular drugs in humans, so only
13 a surrogate nonclinical model will provide a way to
14 compare pathways that lead to intraocular
15 distribution and the exposure that is necessary for
16 bioactivity.

17 Modeling and simulations and the many
18 speakers who spoke about this already in this
19 forum, it's a very powerful tool to integrate this
20 data across the in vitro and in vivo studies. Data
21 from in vitro transcorneal permeation studies, PK,
22 and tissue distribution, and PD studies can be

1 analyzed to develop PK and PK/PD models.

2 When combined with translatable
3 assumptions, this enables sensitivity analyses of
4 product-critical parameters and provides
5 supplemental in silico qualitative confirmation of
6 product equivalence.

7 A comprehensive approach of orthogonal
8 measurements that incorporates early, intermediate,
9 and extended formulation-controlled performance
10 aspects, per the figure that you see in the slide,
11 will provide increasing assurance of quantitative
12 equivalence with supplemental support that is
13 provided by the in silico PK/PD modeling.

14 Each successive quantitative assay that you
15 see depicted in this schematic is progressively
16 reducing layers of residual uncertainty driving
17 towards confirmation of therapeutic equivalence.

18 This collective weight of evidence from all
19 these multiple, orthogonal, and progressive
20 measurements are basically essentially replicating
21 the regulatory process of RLD approval to support
22 the expected equivalence in human efficacy.

1 In conclusion, definitive confirmation of
2 equivalence of topical complex ophthalmics can be
3 provided only when Q3 and IVRT are augmented with
4 biological assays that link API and formulation to
5 their local performance; that is the in vivo
6 biological effect of the site of action.

7 The augmented paradigm for equivalence, as
8 you see in this figure, establishes a comprehensive
9 product performance matrix where Q3 and IVRT
10 testing can be standardized, but augmented with
11 innovative and product-specific functional assays,
12 bioassays, that enable a meaningful correlation of
13 formulation function to in vivo performance.

14 We're here today because we want to
15 mitigate the risks to support the approval of
16 quality generics for complex ophthalmics. This
17 would be achieved by using an in vitro approach
18 that is augmented with biorelevant tools and PK/PD
19 modeling that helps us to mitigate the residual
20 uncertainty that is associated with product
21 equivalence and strengthen the overall conclusion
22 of bioequivalence of a test versus a reference

1 product. Thank you.

2 (Applause.)

3 DR. LIONBERGER: Thank you.

4 The second speaker in our open public
5 hearing is Fubin Wu, representing GessNet Risk
6 Management.

7 **Presentation - Fubin Wu**

8 DR. WU: Thank you, FDA, for the
9 opportunity. First of all, I wanted to let you
10 know I came from a different world. I hope that
11 didn't scare you. I came from the device world,
12 more engineer focused, and you eventually get into
13 the combination product.

14 There is a method I want to introduce
15 today, I think that can really help to solve many
16 of the complex issues we talked about today. With
17 that, I'm going to jump into it.

18 We provide the risk management consulting
19 for the manufacturer of medical device and
20 combination products. One of the common challenges
21 for regulatory science, not only for the drug side
22 of the device or even other agencies, is the

1 manufacturer submit data as required, and then the
2 regulatory agency makes a decision, analyze the
3 data, connect the dots, and make a decision.

4 What is the challenge with that? The
5 challenge is that as the technology evolving
6 becomes more and more advanced, new innovative
7 solutions come to the world thinking about
8 AI-driven solutions, machine-learning technology.
9 Then the data become large and complex. So then
10 that decision to draw based on a bunch of data
11 becomes harder than hard.

12 There's one method, actually, almost
13 particularly designed for solving that kind of
14 problem. It's called assurance case. Think about
15 a scenario where you have a bunch of data, and then
16 you provide it, and say 100 pages or 400 pages, and
17 the data is only getting larger.

18 You present to someone, whoever it is, and
19 try to agree on what you try to present, which is
20 whatever the desirable conclusion you want the
21 reviewer to agree with you. You provide the data,
22 but then what is the rationale of how those data

1 collectively are supporting the top conclusion.
2 And typically in our regulatory framework, we do
3 not particularly ask for that part of the
4 information or that part of the information is not
5 explicitly documented or provided.

6 So assurance case is the way. It is the
7 argument. You can have 10,00 pages of data,
8 whatever it is, and the assurance case can make the
9 connection why those data are collectively
10 supporting whatever the goal you try to achieve or
11 for whatever the conclusion you want a reviewer to
12 agree with.

13 There are certain terminology related to
14 assurance case such as claim, which is really the
15 conclusion you want a reviewer to agree with you;
16 context; assumptions; argument, which is reasoning
17 evidence, which is data.

18 I like this methodology because it really
19 transforms data to be knowledge. Data without
20 explanation doesn't necessarily become knowledge.
21 It's just data. Someone has to review, analyze,
22 and make the connection.

1 Here's an example of how, hypothetically,
2 an assurance case can be. By the way, an assurance
3 case can be a safety assurance case, security
4 assurance case, effectiveness, and efficacy
5 assurance case. It's just whatever the nature or
6 property for a particular product or system you're
7 trying to convey.

8 You can have a top claim in this example,
9 combination product is adequately safe for its
10 intended use, and then you break down into what
11 actually that means. I want to just explain a
12 little bit.

13 When we make that kind of claim, we
14 typically do not have the luxury to have a
15 particular testing report to say, because I have a
16 test, this test report says it is safe. That's too
17 simple, otherwise, we don't need an assurance case.

18 The challenge is complicated. What that
19 means is when we say a combination [indiscernible]
20 product is the same for the intended use, what that
21 means is what actually constitutes sufficiently
22 supporting that claim as true.

1 Then you break down into multiple criteria
2 of whatever the criteria the agency and the
3 industry can agree on. So you can say the drug
4 itself is as effective for the branded drug, and
5 the risk associated with the product is adequately
6 mitigated. There may be other different things.
7 Then we call that sub-claim.

8 The sub-claim can go further down to a
9 level where you are able to connect your specific
10 evidence. So we average down what is the claim,
11 what's the explanation, and what's the data
12 supporting your expectation. Those are the three
13 key elements for our assurance case method.

14 Will you not be able to directly point the
15 particular evidence supporting your claim, then you
16 break that into multiple sublevels until you have
17 specific evidence supporting that. Then
18 collectively, you can build a case. You can convey
19 that story.

20 How do we reason and how do we argue in
21 general, which as we do all the time even with our
22 thinking, we use logic. That's one way to argue to

1 explain something, or we use probability. There
2 could be a scientific study or could be a
3 statistical tool that concludes supporting you are
4 correct. Or we use qualitative. If there are no
5 other methods, then we do whatever we believe is
6 right and let the others challenge why it's not, so
7 that we likely use the qualitative approach.

8 There's also a concept confidence argument.
9 When we break down from the individual claim to the
10 evidence, that's where you actually can explain why
11 is that. You say because this evidence is blah,
12 blah. But then, on the other side, the confidence
13 argument goes to how do you know that evidence is
14 trustworthy, is scientific, is valid? We say
15 that's the confidence argument for that piece.

16 So argument typically is explanation, why,
17 and the other side is a justification why what you
18 said is trustworthy. So when you break down from a
19 top claim to a sub-claim, that's where if you have
20 one claim, and you're saying we have met three
21 criteria as a sub-claim, you need to justify why
22 those three are sufficient to support the top claim

1 if every one of those individually is valid.

2 This is a general format. I did not
3 particularly recommend you have to use a certain
4 format. Whatever it is, the kind of thinking, how
5 you can build a story to convey, I think is the
6 real key, the learning you can get from assurance
7 cases concept.

8 Some of the drug delivery devices such as
9 infusion pump, the CDIH [ph] has actually
10 implemented that assurance case method in the
11 premarket submission. That is very much similar in
12 many different ways to combination products on the
13 device side of it. So your fusion pump is
14 generally fusion. Drug delivery is typically a
15 combination product delivery for a certain
16 particular medication.

17 When we develop guidance on how to
18 implement that assurance case, this is the overall
19 argument structure. The devices are validated,
20 verified, and the risks are mitigated, identified,
21 and then it's adequately reliable.

22 This is an example. I don't have time to

1 go through it, but basically, as a result outcome,
2 this is actually an HTML file. You can use a
3 browser to open it. You can navigate through, and
4 basically, there's a top claim and break down into
5 the lower level. The reviewer can examine
6 individual areas and search by keyword. You can
7 even have a risk of distribution overall related
8 area, and then search by keyword to do a review.
9 This is a tabular format. It's another format.

10 One of the key lessons we have on the
11 device side of the practice in assurance case
12 method, one of the reviewers said, well, even the
13 worst assurance case provide much higher quality
14 data than non-assurance case submission.

15 The other thing is that it would have been
16 very helpful on the device side if we actually have
17 established structure of what do we call the
18 sub-claim, or in other words, the key criteria,
19 when we say the product is safe or effective, what
20 that means.

21 Actually, because we practice in a way we
22 provide whatever is being asked, and the agency or

1 the reviewer is making the determination, when that
2 question is being asked, such as why the product is
3 safe, you may not necessarily know the answer.
4 What does a safe product mean for a combination
5 product, for example?

6 On the other side, the reviewer can use a
7 challenge case method, based on their knowledge, to
8 challenge whether or not the assurance case
9 submitted by the sponsor adequately addresses the
10 top claim or whether the evidence is valid.

11 There are other things you can also read
12 afterwards, but then this is an example for a
13 hypothetical assurance case for the generic drug.
14 I'm not an expert in the drug area, but just to
15 throw an example to stimulate the thinking here.

16 The final thought, I would recommend an
17 assurance case be considered as whether or not it's
18 an ongoing initiative or anything new. I think
19 assurance case can be a powerful tool for
20 communication but also to really allow the industry
21 to [indiscernible] by providing their own
22 rationale, do their thinking, and for the reviewer

1 agency to actually do the check and balance.

2 (Applause.)

3 **Panel Discussion**

4 DR. LIONBERGER: Now we'll move to our
5 panel discussion, so again, I'd like the panel to
6 introduce themselves. Let's start at this end.

7 MS. VENTRELLI: Hi. I'm Molly Ventrelli.
8 I'm regulatory affairs for Fresenius-Kabi in the
9 U.S.

10 DR. STRASINGER: Hello, I'm Carolina
11 Strasinger from the Office of Pharmaceutical
12 Quality and the Office of New Drug Product.

13 DR. RODRIGUEZ: Hi, again. My name is
14 Jason Rodriguez. I'm from the Office of Testing
15 Research and the Office of Pharmaceutical Quality.

16 MS. RODY: Hi. I'm Beth Rody. I am senior
17 director of generic clinical R&D for Teva.

18 DR. RANEY: This Sam Raney. I'm in the
19 Division of Therapeutic Performance within the
20 Office of Research and Standards and the Office of
21 Generic Drugs.

22 MS. NILSSON: Hi, again. I'm Lisa Nilsson,

1 associate director for human factors at Teva.

2 MS. NEWCOMB: Hi. I'm Claire Newcomb, head
3 of human factors at Mylan.

4 DR. MEHTA: Mehul Mehta, director, Division
5 of Pharmacology I, OCP, New Drugs.

6 DR. LUKE: Kiran, you can come up here and
7 join us here.

8 My name is Markham Luke. I'm the director
9 for the Division of Therapeutic Performance in the
10 Office of Generic Drugs.

11 DR. LOSTRITTO: Rik Lostritto. I'm the
12 associate director for science in the Office of
13 Policy for Pharmaceutical Quality.

14 DR. GOBBURU: Joga Gobburu, University of
15 Maryland.

16 MS. D'AGOSTINO-FERLISI: Sandra
17 D'Agostino-Ferlisi, global regulatory intelligence,
18 Apotex.

19 DR. CONNER: I'm Dale Conner, director,
20 Office of Bioequivalence in the Office of Generic
21 Drugs.

22 DR. BROD: Bruce Brod. I'm a clinical

1 professor of dermatology at University of
2 Pennsylvania. In Philadelphia, I kind of live in
3 the clinical world. I'm the director of contact
4 dermatitis and occupational dermatology, and I do a
5 lot of diagnostic patch testing to determine
6 whether patients have allergic contact dermatitis,
7 so live mostly in the clinical world and see the
8 challenges of trying to interpret positive patch
9 test results on the skin. Thank you.

10 DR. LIONBERGER: For this session, because
11 we have diverse topics, we're going to -- sorry,
12 Kiran?

13 DR. KRISHNAN: Hi. I'm Kiran Krishnan.
14 I'm the global head of regulatory affairs at
15 Apotex.

16 DR. LIONBERGER: For this session, because
17 we have diverse topics, we're going to go topic by
18 topic and, at the beginning of each topic, you can
19 then ask the speakers questions. We'll start with
20 the irritation topic, and maybe, Markham, do you
21 want to say a few words to start the discussion?

22 DR. LUKE: Historically, the serum

1 irritation sensation has presented some challenges.
2 The 1999 guidance that was mentioned, I believe,
3 was withdrawn, but continues to be used both in new
4 drugs and in generic drugs as a way to look at
5 comparing irritation sensation. It's old, it's
6 antiquated, but we continue to use it.

7 Walter presented some of the concerns with
8 it, and we thank Walter for that. But we continue
9 to look for new methods to approach and look at
10 irritation sensation.

11 We have Sam Raney. Can I pass the ball to
12 Sam? And also Bruce, who has a lot of intellectual
13 interest in this arena as well.

14 DR. RANEY: Thanks, Markham. I should have
15 clarified that -- this is Sam -- I'm the lead for
16 topical and transdermal drug products.

17 Is Dr. Alberti still with us? No, he's
18 not. Thank you. On European time, okay.

19 Dr. Brod is with us, and perhaps there are
20 others in the audience as well. One of the things
21 that we'd be very interested in understanding is we
22 understand some of the challenges with the existing

1 system. I think one of the key questions we'd like
2 to get out of this session is what would be some of
3 the research that you would recommend that we
4 invest and what are some of the studies that can be
5 done to take us from where we are today to a better
6 way of evaluating this?

7 I want to break that out into two pieces of
8 what does that better world look like, first,
9 specifically focused on transdermal products, where
10 we're trying to make a comparative assessment
11 between two products, a reference product and a
12 generic product, to evaluate whether the perhaps
13 multidimensional aspects of the response that they
14 induce, whether that's comparable or might be being
15 noninferior, and how do we get to where we are from
16 what we're doing today to that point?

17 Actually, a second dimension to that, that
18 is not dealing with transdermal products but with
19 topical products, topical generics, where the
20 formulation of the generic product is different
21 than the formulation of the reference product.
22 What would be some efficient ways for evaluating

1 whether there is a potential implication for a
2 difference in irritation or sensitization if these
3 products are not evaluated in a clinical endpoint
4 BE study?

5 Dr. Brod, I don't know if you'd be able to
6 perhaps begin by commenting on those.

7 DR. BROD: No. Well, those are excellent
8 questions, and I think it sort of highlights how
9 our gold standard for diagnosing irritation and
10 sensitization, which is patch testing, is fraught
11 with a lot of problems. It's messy. It's subjective.
12 It's very subjective in nature, and I agree that we
13 need more studies. We need to figure out a way to
14 objectify whether a reaction is irritant in nature
15 or allergic in nature.

16 There are various histologic type studies,
17 but of course, that's invasive. But even that has
18 difficulty sorting out some of the distinctions.
19 Some of the infrared-type studies, I think, are
20 interesting, and I think that would lend itself to
21 something to study further.

22 One thing I want to point out that I think

1 is very important to try for you to understand is
2 that irritant reactions, when evaluating new
3 potential generic transdermal drugs that come to
4 market, are far and above much, much, much more
5 common than allergic-type reactions.

6 I very much agree that the rating system
7 and the scale is something that should also be
8 studied, and evaluated, and given lots of
9 deliberative thought. Irritant reactions may occur
10 relatively quickly. They're fairly reproducible,
11 but on the other hand, there's a lot of
12 distinctions between different skin types,
13 different genders, the age of the patient. People
14 react very differently. I think that's also an
15 area that we need to study a bit further.

16 I think another area that we need to
17 acknowledge is that we heard from our first speaker
18 that redness is a pretty good indicator, but it's
19 certainly not the only indicator of irritant
20 reaction. So I think another area of study is to
21 look and understand some of the different
22 morphologies of irritant reactions.

1 We saw the old scale has a combination of
2 redness on one side and lots of skin changes on the
3 other side, and I think we need to understand how
4 those two mesh together.

5 Those are just some of the challenges, and
6 I definitely think we also need to -- the 21-day
7 studies were somewhat arbitrary a little bit in
8 nature, and I will take the institutional hit for
9 that because a lot of those studies were developed
10 by the great Albert Kligman, who was a Penn
11 dermatologist who developed a lot of those studies
12 at Penn. But I think those are subject to review
13 as well. There's the potential to sensitize
14 patients if studies are carried out over a
15 prolonged period, and, as I said, irritation can
16 usually be determined pretty quickly.

17 I think one of the things we need to keep
18 in mind is that, in studying these drugs, if we
19 sensitize somebody to the patch or the delivery
20 system, we could be sensitizing them to the
21 vehicle, but we could also be sensitizing them to
22 the active drug, and then there's implications for

1 systemic reaction.

2 I don't know if I've answered your question
3 at all, but the thing I wanted to at least put out
4 there is that it's very complicated. I think I
5 really appreciate the fact that there's going to be
6 some deliberation over this and lots of moving
7 parts.

8 DR. LUKE: Bruce, I want to thank you
9 there. Also, as a practicing dermatologist, I
10 agree with your concerns and also Walter's concerns
11 that he raised, that the scale is, one, nonlinear,
12 two, nonprogressive, the current scale that we use.

13 When we're comparing one product to
14 another, it helps to have a progressive linear
15 scale, whereas linear is possible, so that you can
16 get some notion of bioequivalence. Right now, the
17 scales are done, and the concern is that there
18 might be some arbitrariness to it. Also the fact
19 that it's antiquated and it's only done by a few
20 specific centers around the United States that know
21 how to do this, suggest it's fairly esoteric in
22 nature.

1 DR. LIONBERGER: Maybe we can get the
2 perspective from the generic industry on your sense
3 of the sensitization irritation studies. What are
4 some of the challenges you found in integrating
5 these studies into a development program?

6 MS. RODY: Hi. I think I can comment a
7 little bit. Just based on our experience, I will
8 say that I do agree with the comments that have
9 been made with respect to the scores, that they're
10 antiquated. And I think just recently, as Walter
11 pointed out in his presentation, new scores were
12 adopted in Europe. They've also essentially
13 removed the piece for the sensitization, the
14 challenge phase, due to some of the ethical
15 considerations associated with that.

16 One of the things, I guess, that I found in
17 my experience is that the studies as they currently
18 stand are not very sensitive. It's very rare that
19 we see any of these studies fail, in my experience.
20 Either it's the method itself or perhaps it's that
21 we're not making such a significant change with a
22 generic patch that it would make it more irritating

1 or there would be a sensitization reaction.

2 I even question whether or not -- in
3 certain instances, depending on what changes are
4 made to the generic patch, we have to keep within
5 IIG, of course -- is there a real necessity to do
6 these tests? So from my perspective, that's what I
7 have.

8 DR. RANEY: That's helpful, actually. Are
9 there certain areas -- you spoke about the,
10 perhaps, lack of sensitivity. Do you have any
11 ideas for the kinds of research that it would be
12 worthwhile for us to focus on that would help us
13 kind of generate the evidence to establish a new or
14 different system?

15 MS. RODY: Sure. Yes. I don't have
16 specific recommendations, I would say, today, but I
17 do think it's an area of research that we should
18 invest in with industry and with FDA. I think that
19 there's a real need here because the studies
20 themselves, as have been mentioned, they do have
21 their limitations, and I would think that we could
22 come up with some sort of a more discriminating

1 method. Unfortunately, I don't have something
2 specifically to offer up today.

3 DR. RANEY: We have been contemplating
4 research in this area, very much focused on the
5 scales that I think all of us have spoken about,
6 also looking at better understanding the underlying
7 and molecular mechanisms, underlying irritation,
8 and allergic responses; looking at the technologies
9 that would be more sensitive to discriminating
10 different types of mechanisms that induce irritant
11 or allergic reactions using different kinds of
12 spectral imaging that are more sensitive to
13 differentiating these things; and also using better
14 phrasing and logic to tease apart what contributes
15 to having one score versus another score; and
16 perhaps even having machine learning as more
17 sensitive than a visual observer.

18 So if there's anyone else that has
19 comments, we would welcome you to reach out to us
20 independently and provide comment to the docket as
21 well. This is an area that we're actively
22 interested in researching and moving the needle

1 forward.

2 DR. LUKE: Rik has a comment.

3 DR. LOSTRITTO: Thank you. The comment I
4 have is that you mentioned the IIG. I think in
5 addition to the ingredients, it would be also good
6 to correlate the impact of impurities, leachables,
7 and extractables as well, because even though they
8 may be present in very small amounts, it may
9 contribute or even initiate irritancy or
10 sensitization. So I would think research along
11 those lines would be wise to include those sort of
12 studies, too.

13 DR. RANEY: That's a great idea. Thank
14 you.

15 DR. LUKE: Bruce might have something to
16 add to that as well. Having been working in the
17 cosmetics arena and also from the contact
18 dermatitis field, if you don't have an ingredient
19 in the product, you won't develop an irritant or
20 allergic reaction to it. Right?

21 DR. BROD: No, that's very true. We're
22 talking about reactions to kind of a complex soup

1 when they occur, and we're trying to brainstorm
2 about potential, the holy grail, that will tell us
3 this is the reaction, it's an allergic reaction, or
4 it's an irritant reaction.

5 I think it's good to think along those
6 lines, but I think it's also important perhaps to
7 take a step back and think about maybe the way to
8 discern whether reactions are irritant or allergic,
9 is to be able to have a mechanism to separate out
10 the individual components during the testing
11 process, and actually have an easy way to test
12 patients to those components, break it apart, and
13 determine what, if anything, is causing reaction to
14 occur.

15 Is it the active drug? Is it the vehicle?
16 I think, in doing that, it will also elucidate to
17 us, in many cases, whether it's an irritant
18 reaction or a true allergic reaction. I think we
19 need to break away from the old mold of doing
20 defined readings and think also about doing
21 readings over longer periods of time in certain
22 subsets of patients as well because that actually

1 can be quite helpful in distinguishing between
2 irritant and allergic reactions.

3 I think it's great to try to find that holy
4 grail, but I'm not optimistic necessarily. We've
5 been looking for it for quite a long time. And I
6 don't want to discourage it, but I do think we need
7 to kind of go back to what we do know with clinical
8 experience, using some of those techniques and how
9 we distinguish between irritant and allergic-type
10 reactions. We struggle with this all the time, but
11 I think testing the individual components might
12 need to be a part of this.

13 DR. LIONBERGER: Dale, did you have a
14 comment?

15 DR. CONNER: Yes. We actually have a
16 history of doing something similar to this, and
17 that's with the long and prolonged development of
18 the vasoconstriction assay for steroids.
19 Eventually, we came to adapt a method that was
20 originally intended to measure erythema to do the
21 kind of lack of color, effectively the opposite of
22 erythema.

1 It started out also with all of all of its
2 shortcomings as a human observer trial. That's the
3 way it originally developed because the instruments
4 and technology wasn't developed at the time when
5 McKenzie and Stoughton were originally doing their
6 experiments and publishing.

7 But we quickly became aware that, for these
8 type of purposes, human observer ratings of 3, or
9 4, or 5 points, as Markham pointed out, it's not
10 linear. It's an ordinal scale. The statistics on
11 ordinal scales are always a little difficult,
12 especially when you're doing equivalence.

13 I would say that a lot of that experience,
14 even though it doesn't on its face seem to be
15 exactly the same thing, should go into the thinking
16 of what Sam said, a possible use of instruments or
17 other technologies to read this rather than
18 depending on the human.

19 Now, we all know that the human
20 dermatologist eye is an extremely good instrument
21 as far as clinical evaluation, years and years of
22 training, and you all do an amazing job at

1 assessing clinical status of patients. But I think
2 this requires a bit more technology. To get that
3 linear scale that you're after, you really can't do
4 that with human observer ratings.

5 DR. LIONBERGER: Let's move on to the
6 second topic. So I want to move on to the topic of
7 the device substitution question. Now I'll ask any
8 panelists if they have any questions for the
9 speakers that talked about the device substitution
10 issues.

11 DR. KRISHNAN: I don't have a question but
12 a comment on the issue that is related to -- there
13 are certain things. For example, even we've seen
14 some instances where the labeling may be the same,
15 the steps may be the same, but then it comes back
16 to subjectivity in determining the ergonomics or
17 the differences in design.

18 I think any research work that could be
19 done to make this more objective would really help
20 because, right now, we invest millions of dollars
21 in developing these devices. And then, if we have
22 to start making changes to this, it becomes very

1 challenging. So that's something that could be
2 looked at.

3 DR. LIONBERGER: So you would prefer a more
4 objective measure of, these two devices are
5 similar.

6 DR. KRISHNAN: Or a way for us to
7 determine --

8 DR. LIONBERGER: Unambiguously.

9 DR. KRISHNAN: Yes, because right now,
10 you're almost caught in the gray area, saying, is
11 it okay or not okay, and then you wait.

12 Sometimes also, when we do these human
13 factor studies in terms of analyzing the human
14 factors studies, I'll redo the analysis. So yes,
15 we send in control correspondence. We wait for the
16 agency to come back and tell us. But as we see the
17 number of products, in this case, that are growing,
18 we would appreciate some kind of more clear-cut way
19 to move forward.

20 DR. LIONBERGER: General agreement from the
21 other members of the industry panel, that that's a
22 desired state, to have more --

1 MS. NILSSON: Definitely. It would be
2 easier -- it's hard to say unambiguous.

3 DR. LIONBERGER: Well, unambiguous could be
4 it has to be exactly the same as the brand product.
5 I'm not sure that's what you --

6 (Laughter.)

7 MS. NILSSON: That's not what we would like
8 from a manufacturer's perspective, but the more
9 guidance we can get, the easier it would be to
10 focus our resources at the right place and making
11 sure that we make the best and safest devices.

12 MS. NEWCOMB: I think, from my perspective,
13 when you talk about ambiguity, we need to know what
14 the question is. What is it that we don't want to
15 have ambiguity on? There's a fine line between
16 human subjectivity and no ambiguity. I think
17 that's something that we really need to remember,
18 that we can only understand what a human is going
19 to do by talking and testing with humans, and that
20 is very subjective.

21 DR. LIONBERGER: For the industry members,
22 as you're developing these products, before you go

1 to the final decision, at what point do you
2 integrate some initial human factors studies in
3 your development program, like as you're choosing
4 what device? At what stage in the development
5 would you first do a human factors type of pilot
6 study?

7 MS. NEWCOMB: I guess it depends on the
8 nature of the project that you're developing and
9 how much you know about that type of product
10 already. But it would be very common for us to run
11 early preference-type studies, understanding what
12 the patient type can handle in terms of the device
13 and what their needs are.

14 In a way, you're using your patients to
15 define the needs of the product as well. But when
16 we come to talking about more aligned with the new
17 guidance, then there isn't so much of a requirement
18 for us to look to human factors studies.

19 DR. LIONBERGER: Yes. So that's what I'm
20 asking in your development process. Comparative
21 human factors is sort of at the very end, but
22 before you get into the guidance and the threshold

1 analysis, you are making some decisions. And
2 that's the question; do you use human factors
3 studies as a part of your design, product design
4 and product development processes?

5 MS. NILSSON: We use human factors both as
6 [indiscernible] reviews from the team, but there
7 might also be early formative studies where we're
8 just looking at preferences and similar and very
9 early results. It could be a collaboration with
10 marketing, so it's borderline market research,
11 human factors.

12 But as I said, it really depends on what
13 the application, who the user group is, et cetera.
14 But I think every human factors group in the
15 industry would like to be involved as early as
16 possible in the development and be there when they
17 say we're going to go with this device.

18 DR. LIONBERGER: So Rik?

19 DR. LOSTRITTO: I was intrigued, Lisa, by
20 your comment, where you implied in so many words
21 that if changes you were making were incremental to
22 a device that made it less error prone, easy to

1 use, or labeling eliminated confusion -- I guess I
2 would just challenge that a little bit and say
3 you're dealing with two patient populations, those
4 who have been using the RLD for a long period of
5 time and new patients.

6 Let's say you successfully reduce the
7 number of steps to use it from 10 to 7. It's not
8 necessarily a given that reducing the number of
9 steps is going to lead to better compliance. It
10 may engender more errors of a different kind.

11 That is some of the thinking we apply when
12 we're looking at that, so it's just something to
13 put on the table to discuss.

14 MS. NILSSON: Yes, I totally agree that
15 just because you have few user steps doesn't mean
16 that it's easy to do. Sometimes, this could be
17 much easier because it's more intuitive. So you
18 also have to look at the whole landscape of devices
19 and environments that the user is in.

20 We have a device that we developed 20 years
21 ago. That was before we had iPhones, before people
22 used their smartphones on a daily basis. So people

1 had a different mindset to different things. The
2 whole user environment is different.

3 Then I agree, we have two user groups, the
4 ones that are using the device already, and they
5 should be able to use the new device without being
6 retrained, so it should be intuitive. But I argue
7 that if I give you a pen, and in some cases, you
8 just take the cap off like that, or in some cases,
9 you have to twist it off, you're not really going
10 to notice which way you did it because those are
11 both very intuitive ways for you to take the cap
12 off a pen because you've encountered them so many
13 times.

14 It's the same with a lot of devices we
15 have, that in some cases, if I would go and ask a
16 user, how do you do -- do you pull the cap off or
17 do you twist the cap off? They don't even know.
18 So if I give them another one with a different
19 type, they wouldn't even notice the difference, or
20 they will, intuitive, be able to use it.

21 In some cases, it would be a huge
22 difference. But the biggest difference, I would

1 say, is when you have the new users. If we could
2 have the possibilities to do minor tweaks to the
3 IFU, we might not change any of the user steps, but
4 we might add a tiny explanation sometimes.

5 There's a good example of, after you use
6 the inhaler, you're supposed to tell them to rinse
7 the mouth. If we just tell somebody to rinse the
8 mouth, they would have been, whatever, they're not
9 going to do it. If you tell somebody to rinse the
10 mouth with water after usage, because otherwise
11 they might get thrush, they're much, much more
12 likely to do it.

13 So we wouldn't change the user step. We
14 just want to add that little thing there, or we
15 might want to move a warning from the end of the
16 IFU. So you've done all your steps because you've
17 followed your ST step by step, and then in the end,
18 you realize here's a warning that says, at the
19 beginning, I shouldn't have done a step 2.

20 If we could do those small changes, I think
21 we could make the experience much more pleasant for
22 the user in the end.

1 MS. NEWCOMB: I think that's the
2 conversation that we'd like to have with the
3 agency, is to understand that space in which we can
4 make the user interface more current, more relevant
5 to the user, without impacting the way that they
6 use the device, or indeed, the reference product if
7 they were to switch back as well, and that's
8 something we have to be very cognizant of.

9 But there is an area that I think we do
10 have to play with. And if you're very black and
11 white and say everything has to be word for word
12 the same, picture by picture, the same, then we're
13 missing an opportunity to give the patient the best
14 user interface that we can.

15 DR. LIONBERGER: Other comments?

16 DR. GOBBURU: Yes. So this latest
17 discussion, to me, doesn't sound like a generic
18 topic at all. It's a labeling topic. It has to
19 apply for both the dosing device as well as this
20 one. So I'm not sure if this is anything special
21 there about generic approval. If the labeling
22 language needs to be clarified, but the picture

1 needs to be in color instead of black and white,
2 that applies to both products.

3 DR. LIONBERGER: Dale?

4 DR. CONNER: I had very similar comments,
5 that a lot of times, when you're doing generic drug
6 development, you could do a lot -- because you're
7 years newer and you have newer technology and newer
8 approaches, a lot of people, when they go to make a
9 generic product, could make a much better one than
10 the innovator.

11 But that's not the point. If you do really
12 go full bore in making something much better,
13 chances are, you won't be approved because you will
14 have deviated so much from the generic product that
15 you won't be acceptable. It would be probably a
16 great NDA, but it's not a generic.

17 The other question I had was that you
18 presented a very nice kind of very ordered way of
19 engineering and science of this new product that
20 you're designing. But when you go down the kind of
21 optimal path through your steps, I just wonder
22 how -- you mentioned IP considerations, but how

1 often does that kind of change you to a less
2 optimal path through your development?

3 We all imagine the patent issues are always
4 a problem, especially with devices. How does that
5 really affect and constrain you proceeding through
6 this well-ordered kind of design philosophy?

7 MS. NILSSON: I don't have any statistics
8 on it, and I work mainly with sterile injectables.
9 But I would say at least in 50 percent of the
10 times, we cannot choose a device that is as similar
11 as we would prefer to be sure that we could just
12 sail through it, but because it's IP restricted, we
13 have to go something that is slightly different
14 somehow, so it's quite often. That will force you
15 to do slight changes to the IFU because there are
16 no options.

17 DR. KRISHNAN: Even if it's not the IFU,
18 for the exact same reason, there are copyrights or
19 patents, as a result which then you would need to
20 tweak the shape. There could be, like, minor
21 tweaks. And that's where it becomes a challenge
22 for us.

1 DR. VENTRELLI: Yes. We do similar,
2 syringes, auto-injectors, and I would say, when you
3 look at something as complicated as an
4 auto-injector, almost 100 percent of the time,
5 they're covered with an entire thicket of patents
6 that you have to get around and have to make
7 changes.

8 Simple syringes and those things are a
9 whole different story, but from an auto-injector
10 perspective, you absolutely have to design around
11 all the patents, and you have to start that at the
12 very beginning so that you know what kind of an
13 auto-injector to go for, and you can design your
14 user needs to fit that in the rest of the design
15 verification and validation.

16 DR. LIONBERGER: Any other?

17 DR. BROD: I think the other thing, too, to
18 think about going forward, one of the disadvantages
19 of the skin is you can see it. Somebody takes a
20 pill, a branded pill and a generic pill, and one
21 causes a little more stomach irritation than the
22 other, you're not going to notice it.

1 So I think one of the things that I would
2 just urge to think about going forward is what
3 constitutes clinically meaningful irritation on the
4 skin, and then try to develop a scale that reflects
5 that as well going forward. I don't have the
6 answer to that now, but I just throw that out there
7 as well.

8 DR. LIONBERGER: So any further comments on
9 the device topic?

10 (No response.)

11 DR. LIONBERGER: Then let's move
12 on -- Kiran has a presentation on bridging and
13 globalization, so any clarifying questions for
14 Kiran's presentation?

15 (No response.)

16 DR. LIONBERGER: I have a clarifying
17 question. If you're able to get enough product to
18 do bridging, how different is that from the amount
19 of product you need to do the full bioequivalence
20 testing on the product from the U.S. market if it's
21 just a -- something specific in that case, where
22 it's access to amount of product?

1 DR. KRISHNAN: if you look at the -- like,
2 for example, for the purpose of doing bridging, you
3 probably can get away by doing dissolution work and
4 characterization work, you don't need that many
5 samples, but when you go through a bioequivalence
6 study, you need not just a sample, but obviously
7 the ratings as well. It's almost 5x of the sample
8 that you need.

9 For what you need to do, looking, testing,
10 you need 5x so that goes in rating. So you need a
11 lot more for doing a BE study in those instances.

12 DR. LIONBERGER: In some cases, it would be
13 possible to obtain enough samples to do a bridging
14 study, but it would be a significantly less burden
15 than obtaining the number of samples you need to do
16 a whole BE study?

17 DR. KRISHNAN: That is correct.

18 DR. LIONBERGER: Rik, question?

19 DR. LOSTRITTO: Two questions. One of the
20 things I worry about in the sequential thing like
21 that is a phenomenon called creep, where if you
22 have this product equivalent to the next, and the

1 next, and the next, little changes accumulated over
2 time, and it won't be equivalent to the first one.
3 I'd ask you how you would deal with that issue.

4 Also, in one of your slides, you said to be
5 media dissolution. I hope that does not include
6 surfactants. And if it does, how would you justify
7 that to show equivalency when surfactants really
8 normalize out so many factors?

9 DR. KRISHNAN: If I understand your first
10 question, you're talking about the shift. Again,
11 these are instances where you're talking about an
12 RSB that is available in the U.S., and the same
13 reference product is available in Canada by the
14 same manufacturer. We have seen, in many
15 instances, for some of these newer products that
16 are coming out, some of these complex ones and the
17 newer ones, they don't have different formulations
18 in different markets. It's the exact same product
19 made to the exact same cycle.

20 So those are the specific products. I
21 mean, I'm just giving you one of those examples,
22 but if you look at the guidances of the

1 requirements in Canada or in Australia, that is
2 exactly one of the requirements. You have to
3 demonstrate the sameness of the product.

4 That probably would take care of your first
5 question. And I'm sorry, I missed your second one

6 DR. LOSTRITTO: I'm sorry. You mentioned
7 dissolution 3 media.

8 DR. KRISHNAN: Yes.

9 DR. LOSTRITTO: That's a blanket statement.
10 That could be a good thing or it could level out
11 changes that are important, depending upon the
12 media, and so forth, and other conditions.

13 DR. KRISHNAN: But you are just comparing
14 the same two products, so again, these conditions
15 are based on the requirements to do the multimedia
16 dissolution profile.

17 DR. LIONBERGER: Dale?

18 DR. CONNER: I have actually a question
19 about Canada and Australia. You've held them up as
20 jurisdictions that are similar to the U.S., except
21 for in references for what they considered
22 generics. Even though they're similar, their

1 systems, and their regulations, and their histories
2 are not necessarily the same as the U.S.

3 DR. KRISHNAN: That is correct.

4 DR. CONNER: I think, when you kind of
5 throw them up as examples and say you should be
6 doing exactly this, one of the things we were
7 constantly getting into, I think you mentioned,
8 international harmonization as well, is that a lot
9 of countries that seem very similar and have
10 similar ideas about the science don't necessarily
11 have the same regulations. In fact, that word
12 "generic" doesn't mean the same thing in a lot of
13 countries as we have it here in the U.S.

14 So even though they are superficially
15 similar, there are sometimes very little things
16 that kind of are differences, and they may be not
17 insurmountable differences, but difficult
18 differences to overcome.

19 So if you're trying to harmonize a lot of
20 these countries, sometimes they have to change
21 regulations or even laws, and that's not a small
22 matter. Having been involved just in the U.S. and

1 changes in regulations, it's a good 10 or 15 years
2 sometimes for a major regulation change, so there's
3 that.

4 We've had experience in the past -- I don't
5 know how it is today -- where the same company, the
6 same RLD company or big pharma company, produced
7 allegedly the same product with the same name, but
8 they were different. They contained the same drug
9 substance or substances. They may have even been
10 manufactured in the same factory, but they were
11 clearly, by the company's admission, not the same
12 thing, and so we discovered that only much later.

13 So how do you deal with those kind of
14 things where you're assuming same company, same
15 brand name, same drug substance, manufactured in
16 roughly the same place? How do you provide
17 assurance? If you're a generic sponsor and you
18 don't have access to any of their secret,
19 proprietary information, how do you go about
20 assuring regulatory agencies that you're really
21 using the same reference?

22 DR. KRISHNAN: I think that's a great

1 question. I think that's part of what we are
2 requesting that the NC look into this issue to see
3 if there's an opportunity to use or determine what
4 is the criteria to establish that sameness, if you
5 may.

6 Now, to your point, if there are
7 differences -- I mean, obviously, these guidances
8 dictate a battery of tests, and the expectation is
9 these tests would be able to highlight the
10 differences, if any. Again, that's something that
11 again is more product specific and it's not
12 something that could be applied in --

13 DR. LIONBERGER: I want to link this to
14 something that came up earlier in the day. We were
15 talking about BCS class 3 drugs, and the question
16 of deformation technologies. I think there is a
17 linkage here between the type of things that you're
18 asking on bridging and the technologies that
19 someone would use to deformulate a -- I want to
20 find out if I'm Q1/Q2 to a BSC Class 3 drug.

21 So I would appreciate some of the comments
22 on the industry on your skill at deformulating

1 this, and also maybe Jason from DPA, because I know
2 that you guys do some forensic-type testing on some
3 of the biostudy samples to detect products, to show
4 that they're different.

5 I'd appreciate comments on the state of the
6 art of deformation and forensic analysis and
7 analytical methods of, say, solid oral dosage form
8 products. So please?

9 DR. KRISHNAN: Obviously, deformation
10 itself is a huge science or activity that happens
11 these days. Now, there are techniques that are
12 available today. Of course, we looked at MDRS as
13 one of the examples earlier, but then you have
14 Raman spectroscopy, fingerprinting that's there.

15 Now, the deformation is something that
16 the generic industry does. Now, obviously we talk
17 about the solid oral dosage forms, but that is
18 something that we do as a standard practice for
19 ophthalmics and nasal sprays because that's the
20 basis on which we asked for the Q1/Q2
21 correspondence.

22 Now, solid oral; from our experience, we do

1 believe that there's enough solid state
2 characterization tools available out there to
3 understand not just the qualitative composition,
4 which is obviously known a bit more importantly
5 than the quantitative composition.

6 DR. LIONBERGER: Jason?

7 DR. RODRIGUEZ: From the FDA lab
8 perspective, some of the areas that we have dabbled
9 in as needed, based on different projects,
10 analytics, in addition to Raman, which has already
11 been mentioned, there is SCM Raman. There is also
12 cyro SCM. So a lot of these microscopic techniques
13 and morphology have been mentioned a couple of
14 times.

15 Truly, since it's both a physical
16 characterization and a fingerprinting technology,
17 it's something that is really powerful when you're
18 looking at some of these, and you're looking at
19 ophthalmics, also transdermal drug delivery
20 systems.

21 One of the areas as far as laboratory
22 testing goes as well; since it was discussed

1 earlier, maybe there's some product out there, some
2 residual solvent in the manufacturing. We've also
3 looked at residual solvents of transdermal drug
4 delivery systems as well.

5 From a laboratory perspective, one of the
6 things that we care a lot about actually is, at
7 first, begin given a target of what are you looking
8 for as opposed to having a wide range of things you
9 could see, because then it leads you off a
10 different and winding path.

11 But the technology is there so long as we
12 have an idea of what we're going to look for, what
13 property, what ingredient, what impurity, so in
14 that nature.

15 DR. LIONBERGER: Any other comments on the
16 bridging products topic?

17 (No response.)

18 DR. LIONBERGER: So let's move on and talk
19 about the application of Bayesian methods to
20 generic drug analysis. I'm not sure we have the
21 complete experts that we need to give full comments
22 on, but I want to give the panel at least some time

1 to ask Joga some questions about this. So Markham?

2 DR. LUKE: Yes. I have a comment. You
3 mentioned that, using the ANDA studies as a prior,
4 one of the fundamental tenets to using Bayesian
5 approach is that the priors have to be declared,
6 a priori, that you're going into it with Bayesian
7 approach. So quite often, an NDA may have led up
8 to it; the two registration studies may not have
9 been the only studies.

10 So a Bayesian approach usually takes into
11 account the totality of all the studies that were
12 conducted, including the failed studies. And the
13 failed studies would then have to be factored in as
14 priors as well, and plus the lack of a priori
15 declaration would lead to a concern of using those
16 NDA registration studies as priors; just a comment
17 along those, and if you want to respond, please.

18 DR. GOBBURU: My specific proposal is the
19 FDA says that, whatever you want to do, do it and
20 accept that criteria because, otherwise, it'll be
21 chaos for every company to compute that. They can
22 come and negotiate it like any other guidance, but

1 the FDA has to put their foot forward on that one.
2 We can argue about it. We need probably a detailed
3 session. Everybody, when they talk about Bayesian,
4 they keep, oh, what about the failed trials? What
5 about the failed trials? They had no bearing on
6 the approval because you're approved based on the
7 efficacy, not based on the failed trials.

8 So even in the decision-making, you have
9 looked at it, but you have not weighed on the lack
10 of efficacy from those trials, so how can you use
11 that against somebody else now?

12 We can argue about the technicalities, but
13 if generally that idea is appealing, to me, it's
14 worth pursuing because we're talking about research
15 opportunities. We're not talking about changing
16 the law.

17 DR. LUKE: If I could respond to that, I
18 think the issue about Bayesian is that it's the
19 totality of the evidence that leads to a Bayesian
20 approach as opposed to the non-Bayesian approach
21 where you're allowed to start a new study afresh,
22 and you're looking at p values specifically from

1 that study or the two studies that you're getting
2 at for registration. You can send in the other
3 study if they will look at it, but the fact that
4 you failed in the p value does not factor into the
5 registration piece.

6 DR. LIONBERGER: Dale and Mehul?

7 DR. CONNER: There were a lot of things
8 that confused me about your talk, and I think a lot
9 of it was that you seemed to be mixing up NDA and
10 ANDA concepts.

11 So one question is, if you're developing or
12 trying to get a generic drug approved, and you're
13 going to use NDA data as your prior, as your
14 Bayesian prior, how do you get right of reference
15 to that data? Because that data belongs to
16 somebody else, and as a generic sponsor, that owner
17 is not going to be very cooperative because you're
18 essentially taking away their market share. So
19 they're not exactly going to hand over the rights
20 to use that data.

21 DR. GOBBURU: That's why I said FDA will
22 set the rules. You do set the rules by giving a

1 guidance saying that you want 80 to 125, you want
2 this kind of in vitro, you want F2. Those criteria
3 are set by the FDA. What is wrong in being
4 specific about the prior that a sponsor can use to
5 design their trial and drive the statistics?

6 DR. CONNER: You would have to get access
7 from the owner. We don't have any choice about
8 that. If you were a company, you've designed and
9 produced a product. You've paid for the studies
10 that get that product approved. You own that data.
11 And the FDA has access to it, but we don't own it.
12 We can't just use it for whatever we want.

13 DR. GOBBURU: But most of those studies are
14 published, too. You don't need individual data.
15 Why do you need individual data? I have the mean
16 [indiscernible] and the variability, and these
17 details about the design. I can develop product
18 from that.

19 DR. CONNER: I've had the privilege over
20 the years of looking at data that was submitted to
21 the FDA, which we have access based on our
22 function, have access to everything, including the

1 ability to go in and inspect, look at the original
2 lab books, or data, or whatever, computer data.
3 I've also seen those same studies published in
4 peer-reviewed journals, and the two studies don't
5 look anything alike. When you look at the
6 peer-reviewed information, you just simply focus on
7 the positives and act like the negatives don't
8 exist.

9 That experience of working at FDA has made
10 me very -- I don't want to admit this in public,
11 but has made me extremely distrustful of
12 peer-reviewed data because I know it's the same
13 study done by the same people, but it doesn't look
14 at all the same when you have access to all the
15 data.

16 DR. GOBBURU: So tell me this. How did you
17 get the partial AUCs from [indiscernible] without
18 the brand data? When we come up with a guidance
19 for using a partial AUC for a complex or modified
20 release product, where the heck would you get
21 the --

22 DR. CONNER: We're looking at individual

1 sponsors --

2 DR. GOBBURU: No. This is before generics
3 were approved.

4 DR. CONNER: Yes.

5 DR. GOBBURU: So you have to rely on RLD.

6 DR. LUKE: Can I put a positive spin on
7 Bayesian?

8 (Laughter.)

9 DR. MEHTA: I've been waiting this whole
10 day for some discussion on this. No. To somewhat
11 on Dale's line, we do say the overall findings of
12 safety and efficacy of a new drug, a general
13 knowledge that can be utilized by the generic
14 industry, and that's how we approved generics. So
15 are you suggesting that, within that framework,
16 this information also benefitted from that
17 category, and then say that you don't need to worry
18 about legal challenges or ownership of data?

19 DR. GOBBURU: Well, yes, because if we are
20 not convinced that the availability of a particular
21 product is of public health concern, none of what I
22 said applies. If we're talking about -- I'm

1 talking about nontrivial, serious indications where
2 there is a need for the generics and something has
3 to be done for those.

4 DR. MEHTA: I clearly hear you, and the
5 scientific part of me really gets excited, but we
6 need to get our lawyers to just say yes to some of
7 this. The other part quickly is changing the
8 second half of your suggestion, but if I understand
9 correctly, you're saying that, through PBPK or some
10 methodology like that, you established surrogacy.

11 DR. GOBBURU: Yes.

12 DR. MEHTA: Then once that is established,
13 then forget about asking for same surrogacy
14 demonstration again.

15 DR. GOBBURU: Yes. That's right.

16 DR. MEHTA: So that is again going back to
17 the line of question or concern that Dale is
18 expressing. Who owns that?

19 DR. GOBBURU: Hold on. No, no. Hold on.

20 (Crosstalk.)

21 DR. GOBBURU: Any 505(b)(2), including
22 cardiovascular, for example, you don't ask for CHF

1 studies for 505(b)(2)'s? You demonstrate angina,
2 you demonstrate blood pressure lowering, and I will
3 give you all indications.

4 DR. MEHTA: Yes.

5 DR. GOBBURU: Where did you get the rate to
6 use the correlation from the original NDA?

7 DR. MEHTA: So again, that determination
8 was made and that relied --

9 DR. GOBBURU: It's the same legal
10 expectations as far as I can see.

11 DR. CONNER: There is kind of a legal
12 difference when 505(b)(2) -- this was discussed a
13 lot, I think, in public and probably amongst FDA,
14 when 505(b)(2)'s first started to become popular,
15 that the 505(b)(2) uses the FDA finding. They
16 don't reach into the application and take the data.
17 They use the FDA decision, which is of course
18 public, as their basis.

19 They are not allowed to use whatever data
20 they want out of somebody else's application; in
21 other words, reaching into the application, picking
22 out data, and using the study. They used the NDA

1 decision on that.

2 DR. GOBBURU: I am glad we are talking
3 about this. Then you guys come up with a path such
4 that for those kinds of needy products where the
5 hurdle of proving to be a generic is very high,
6 open that by saying that a 505(b)(2) type path is
7 okay? Right?

8 **Closing Remarks**

9 DR. LIONBERGER: So we are coming to an
10 end, so I thank everyone for the discussion. I
11 think the last point illustrates that for generic
12 drugs, there's this very complicated, scientific,
13 and regulatory interplay that we have to navigate
14 as we figure these things out, but that's part of
15 what we do across all of the things related to
16 bioequivalence.

17 We'll definitely have more discussion as we
18 look into this area further, and I think we want to
19 have maybe some more specialized discussion with a
20 broader group of people who have some deeper
21 expertise in this as we discuss this further. I
22 think that's a great suggestion for something to be

1 thinking about.

2 So it's now my responsibility to close out
3 this meeting, so I'd like to express my
4 appreciation for everyone in the audience, both the
5 people here in person and those on the webcast,
6 we're very appreciative of your interest in this
7 topic and your attention to the presentations. And
8 we hope that if this has spurred you to have any
9 comments, that you go ahead and submit them to the
10 docket. You have about one month left for that
11 docket, for your written comments. We value those
12 written comments, so please submit them.

13 I'd like to thank all of our speakers, both
14 from inside FDA and our external experts, for
15 providing very triggering, very challenging,
16 thoughtful discussions. I'd like to thank the
17 panelists for participating in this and really
18 showcasing the challenges that face the interface
19 between the science and the regulatory aspects of
20 generic drug development. I think that's what
21 makes it consistently interesting to work here, and
22 I think this discussion is very helpful to us as we

1 try to formulate what our research scientific
2 priorities are going forward.

3 This is a meeting, and I'd like to thank
4 all of the staff in ORS that really helped organize
5 this meeting, like Stephanie Choi for leading the
6 organization of that, making sure of all the
7 logistics work, getting all of our speakers, and
8 our rooms, and all of the staff in ORS who
9 volunteered and participated to run the AV
10 logistics, to run the check-in desk, to prepare the
11 binders for you. All of that is staff from my
12 office who worked extra hours to make sure this
13 happened, so I want to give them all a round of
14 applause for their effort in making this meeting be
15 very successful.

16 (Applause.)

17 DR. LIONBERGER: The other FDA staff who
18 made the logistics are the Great Room staff that
19 have this wonderful room available for us and make
20 everything work very smoothly for us. I thank also
21 our communication staff and OGD for helping
22 publicize this meeting within FDA and externally.

1 So what we're going to do is take back the
2 comments from this meeting, the comments to the
3 docket, and internally within FDA formulate our
4 regulatory science priorities for the next year.
5 You'll be seeing the results of this posted in the
6 fall.

7 As I look at this meeting, I think there
8 are a lot of interesting things that I think will
9 be showing up in there. I saw a lot of questions
10 related to various aspects of the excipients in the
11 pharmaceutical formulation. They showed up in our
12 questions on the solid oral BCS products, the fed
13 bioequivalence study questions, the analytical
14 methods to characterize the excipients in complex
15 products, as well as the excipient effects on the
16 transdermal irritation and sensitization.

17 So I think one big theme that you take away
18 from here is the attention that we have to pay both
19 as product developers, but as regulators, and our
20 scientific understanding to those inactive
21 ingredients. Certainly excipients is maybe better
22 terminology in the product, and I think that's

1 something, and we'll be thinking about how to
2 integrate that into -- because I think we also
3 already have research that touches on a lot of
4 those in a lot of areas, but to be more explicit
5 about those aspects of important issues related to
6 that.

7 The other thing I noticed is a lot of
8 questions about the devices, both the delivery
9 mechanisms and the interfaces for the drug device
10 combinations. As we look at the landscape of the
11 newly approved products, a big chunk of those ones
12 where we're still developing our standards or have
13 some device component to them. So that's an
14 important aspect to really work on, both the
15 science of the delivery and the interface is so
16 much the takeaway.

17 Also, there's a lot of interest in the
18 newer modeling simulation data analytics methods.
19 We heard that in our Bayesian discussion here,
20 developing the ecosystem around that, questions
21 about method verification, validation, how to
22 provide clear pathways for how companies can use

1 these in their submissions with the appropriate
2 confidence in FDA that they're doing the right
3 thing in the model; so lots of things to take home
4 from here.

5 Again, the docket will remain open. Please
6 send your comments in on these issues as we're
7 going forward, and I would like to thank everyone
8 for their participation, and now, the meeting is
9 officially closed. Thank you very much.

10 (Applause.)

11 (Whereupon, at 4:28 p.m., the meeting was
12 adjourned.)

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