GDUFA 2012 REGULATORY SCIENCE INITIATIVES
Part 15 Public Hearing

May 20, 2016

A Matter of Record
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FOOD AND DRUG ADMINISTRATION

Generic Drug User Fee Amendments of 2012
Regulatory Science Initiatives:
Request for Public Input for FY 2016
Generic Drug Research
Part 15 Public Hearing

Friday, May 20, 2016
9:04 a.m. to 4:15 p.m.

FDA White Oak Campus
10903 New Hampshire Avenue
Building 31 Conference Center
The Great Room (Room 1503)
Silver Spring, Maryland

Meeting Roster

Gordon Amidon
University of Michigan

Bahman Asgharian
Applied Research Associates, Inc.

Amy Barton Pai
Albany College of Pharmacy and Health Sciences

James Brasseur
University of Colorado

Diane Burgess
University of Connecticut

Stephen Byrn
National Institute for Pharmaceutical
Technology and Education (NIPTE)

Michael Fischer
Brigham & Women's Hospital

David Gaugh
Generic Pharmaceutical Association (GPhA)

Ajaz Hussain
National Institute for Pharmaceutical
Technology and Education (NIPTE)

Robert Lionberger
Food and Drug Administration

Kenneth Morris
National Institute for Pharmaceutical
Technology and Education (NIPTE)

Eric Munson
Food and Drug Administration
National Institute for Pharmaceutical
Technology and Education (NIPTE)

Nikunjkumar Patel
Simcyp

James Polli
University of Maryland, School of Pharmacy

Chetan Pujara
Allergan

Russ Rackley
Mylan Inc.

Tracy Rupp
National Center for Health Research

David Schoneker
IPEC Americas

Catherine Sherwin
University of Utah School of Medicine

Duxin Sun
University of Michigan

Kathleen Uhl
Food and Drug Administration

C O N T E N T S

C O N T E N T S (continued)

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C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

DR. LIONBERGER: All right. Good morning, everyone. Welcome to both the attendees in the conference center and those of you viewing the hearing through the live webcast. My name is Dr. Robert Lionberger. I am the Director of the Office of Research and Standards in the Office of Generic Drugs. I'd like to welcome you to this Part 15 hearing, Generic Drug User Fee Amendments of 2012 Regulatory Science Initiatives: Part 15 Public Meeting, Request for Comments.

So I will be the presiding officer today, and we have a distinguished panel of experts from FDA to listen to the presentations. The purpose of the public meeting today is to seek input from a variety of stakeholders -- industry, academic, patient advocates, professional societies, and any other interested stakeholders -- as we fulfill our requirements under the GDUFA agreement to develop a list of regulatory science initiatives for generic drugs.

We're going to take the information that we learn from this public meeting, in addition to submissions to the docket and other sources of information, as we develop our 2017 regulatory science plan.

So before we begin, I want to go over a few housekeeping announcements. First, please turn off any mobile devices as they may interrupt with people being able to hear the meeting. We've asked that all attendees sign in so we can keep you up to date on the research program. The meeting will run until approximately 4:30 today.

We'll be having one 15-minute break in the morning and one 15-minute break in the afternoon, as well as a lunch session. The restrooms are located outside the main entrance to the conference room. And there will be a lunch break from approximately noon to 1:00 p.m., and there will be food and beverages available for purchase in the lobby.

So now I'd like the FDA panel members to introduce themselves. And we'll start with my

supervisor, Cook Uhl.

DR. UHL: Good morning. Cook Uhl, Kathleen Uhl, the director of OGD.

DR. CONNER: I'm Dale Conner, acting director, Office of Bioequivalence in the Office of Generic Drugs.

DR. HOLQUIST: Good morning. Carol Holquist. I'm the acting deputy director for the Office of Regulatory Operations in Office of Generic Drugs.

DR. TOUFANIAN: Good morning. I'm Maryll Toufanian, deputy director of the Office of Generic Drug Policy.

DR. BUHSE: Cindy Buhse, director, Office of Testing and Research, Office of Pharmaceutical Quality.

DR. BOAM: Good morning. Ashley Boam, acting director, Office of Policy for Pharmaceutical Quality in the Office of Pharmaceutical Quality.

DR. BARRATT: Ruth Barratt, Office of Translational Science at CDER, science advisor.

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DR. FRIEDMAN: Rick Friedman, deputy director, Office of Manufacturing Quality.
DR. KORTEPETER: Cindy Kortepeter, Division of Pharmacovigilance, deputy director, Office of Surveillance and Epidemiology.
DR. PINHEIRO: Simone Pinheiro, acting deputy director, Division of Epidemiology I in the Office of Surveillance and Epidemiology. Good morning.
MS. PEREZ: Good morning. I'm Gisa Perez, branch chief at the Division of User Fees Management at Generics Branch.
DR. STODART: Good morning. Brenda Stodart, CDER Small Business and Industry Assistance with the Office of Communications, CDER. Thank you.
Opening Remarks – Robert Lionberger
DR. LIONBERGER: I'd like to thank all of our panel members for giving their valuable time and spending the day here to listen to your presentations and provide input into our regulatory science planning.
So today we have an agenda of 19 speakers in

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the scheduled presentation slots. I will speak first and give an overview of our regulatory science program and set the stage for the input that we're looking for.
In order to keep to the agenda, I want to go over some ground rules. First, this meeting is informal. Rules of evidence do not apply. No participant may interrupt the presentations of another participant.
Only the presiding officer and FDA panel members will be allowed to question a presenter. FDA may recall a presenter for additional questions at the end of the meeting, assuming time allows and the presenter remains available.
Public hearings under Part 15 are subject to FDA policy and procedures for electronic media coverage of FDA public administrative proceedings. Representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including the presentations of speakers today.

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The meeting will be transcribed, and copies of the transcript may be ordered through the docket or accessed on our website approximately 30 days after this meeting.
Each speaker will have approximately 10 minutes to present. And after each speaker presents, five minutes will be allotted to the FDA panel members to ask questions. So we will ask questions, really, to try to get people to focus on what you want us to do and help on the input, is the main purpose of the questions. So if you, in your presentation don't tell us what you want FDA to do, I think you can expect that question from our panel.
Please remember that the meeting is being transcribed, so we want all the panelists to use the microphone when speaking. If we ask you a question, speakers should also submit their responses asked by the panel members to the docket. If a speaker ends early, we'll move on to the next speaker and leave more time for panel questions.
We'll have a timer light for the speakers to

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know when to begin their presentation, which will be green, and when to stop, which will be red. The yellow will indicate a two-minute warning for the speakers.
This meeting is being webcast live, but it's not an interactive webcast. So if you're listening to the webcast, you won't be able to ask any questions or speak in any way.
For those of you who did not register to make an oral presentation but would still like to comment on what you've heard or what you think we should do in our regulatory science program, you may submit comments to regulations.gov. It's docket number FDA-2013-N-0402. So because of that, this hearing is not your last opportunity to comment.
The docket will be open until June 17th, and we strongly encourage all interested parties to comment. To submit a comment with confidential information that you do not wish to be made publicly available, you can send your comments as a written paper-only submission and indicate that it

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contains confidential information. And this is detailed in the Federal Register Notice.

Given the agenda, we ask that each speaker keep to your allotted time so we can keep on schedule and end on time and meet our breaks and lunch schedule.

I want to thank everyone for your interest in the generic drug program and your participation today. We look forward to a very productive public hearing. So we'll now begin with the presentations.

So to start the meeting, I'm going to give an overview of where we are with the GDUFA regulatory science. And really, this is looking back. This is our fourth public meeting, and so it's really a look-back at the whole aspect of what we've been doing and what some of the impacts are to really give a context for the comments now in terms of that.

So this is part of our GDUFA regulatory science process where we prepare a yearly list of research priorities with input from all

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stakeholders. The results of last year's input, our FY 2016 priorities, were post-market evaluation of generic drugs, equivalence of complex products, equivalence of locally-acting products, therapeutic equivalence evaluation and standards, and computational and analytical tools -- a strong scientific foundation for the generic drug program.

As we've been implementing this, we implemented this mainly through both internal and external research collaborations. We have approximately a hundred ongoing research collaborations that come out of these regulatory science inputs. So we're partnering with scientists around the world, leading experts, engaging them to build a strong scientific foundation for the generic drug program.

Under GDUFA, this has really allowed us to scale up the scientific foundations to approximately 10 times the size of the pre-GDUFA effort that FDA was able to make in generic drug regulatory science. In addition to external collaboration, it supports work in our FDA labs; it

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supports post-doctoral fellows, both in our offices and our laboratories, who do a lot of the internal activities.

Linked into this, the office I lead in OGD, the Office of Research and Standards, we manage most of these research activities and we really try to link them in to the development of our guidances and our responses to questions that industry asks through the controlled correspondence process to pre-NDA meetings.

So the results of the regulatory science research feed into the standards for generic drug approval and evaluation that FDA uses. So we try to have a very strong link with that, and I'll try to point out that as we go through the program.

To give a sense of how much we've increased because of the GDUFA resources that have been supplied to regulatory science here, from looking back to the three years prior to GDUFA, you can see there's about a tenfold increase in the regulatory science activity that OGD has been conducting because of GDUFA. And this leads to -- as we begin

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these projects, each year we award new projects. Many of them are multi-year projects, so there's a large number of projects that are under management. So we've been continually growing the program.

Now, by the fourth year of the program, we're reaching approximately a stable plateau of activity. But there's been a huge scale-up in activity, a large number of resources. But I want to talk today about some of the impacts that come out of this research activity.

As we do that, and I'll come back to these at the end when we're looking for comments, the areas of impact of our regulatory science program are generic access in all product categories. This is a strong focus. It's critically important to both the industry and the American public that generic products be available wherever possible.

As we go through today, you'll see that even given the great success of the generic drug program, reaching I think it's 88 percent of the prescriptions dispensed being generic products, still in that remaining 12 percent there are a

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large number of very complex products without generic drug competition. And that's a big focus of the access aspect of our regulatory science program. And if you think about the return on investment of that, each one of those complex products is probably a billion-dollar market.

So everything I'm going to be talking about in terms of complex product access, each one of those represents probably at least a billion dollars in savings to the American public a year if generic products are available in that category. So that's the scale of impact that we're talking about.

If it's not a billion dollar-impact, it probably doesn't make it even into this presentation. So there's still very significant areas where the scientific challenges prevent access to generic products, and we're working very diligently and collaboratively to address those.

The second area of impact is in confidence in generic drug substitution. As we've moved from an environment when I first joined FDA in 2003,

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about 50 percent of the prescriptions dispensed were for generic drugs, to where we're nearing 90 percent.

So that's a much bigger responsibility for both FDA's generic drug program and the industry that's providing that. You're providing the drugs that almost everyone is taking for almost every condition that they're being treated for.

So it's important that there be strong confidence in the products that we're producing, the regulations that are governing them, that people know that they'll be substitutable. And that's what the industry intends. That's what FDA believes when we approve your products.

So there's a strong research focus on identifying areas and research that can sustain that confidence. If you don't have confidence, it's a very unstable situation, given the great responsibility for that large part of the pharmaceutical products that the American public uses.

The third impact is really developing the

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tools for both product development and product review. So these could be computational, modeling tools. Yesterday we had a day-long workshop on oral absorption modeling. Still, solid oral dosage forms are the vast majority of generic drugs. So tools that predict what happens in your bioequivalence studies that aid your formulation design are essential to the efficient development of generic drugs and the review of those products.

But these tools also touch more complex products and analytical and computational methods across the scope. And this is an area where there's huge benefit to industry in using the best available tools, and as I said, by engaging with leading pharmaceutical scientists who bring that information into our review processes.

So when we meet with you on a pre-NDA meeting on a complex product, we've also been engaging with experts in that area as well. So we're able to really be on the leading edge of science as we do that, and I'll talk about some examples where that's led to recent approvals of

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generic products.

So as I said, the success of generics is a large fraction of dispensed prescriptions and the limited cost, but there's still a lot of things on the table.

As we move toward translating the regulatory science results into generic drug applications and approvals, one way we do this is through the bioequivalence guidances and the product-specific information. And you can see that the number of guidances is growing each year under GDUFA. We're maintaining this, and we project that this year we'll produce even more than the year before.

But one thing that you don't see in just looking at the numbers is that the fraction of these guidances that are for complex products is increasing. So we have about 1500 guidances currently posted. The initial surge of that was capturing a lot of the immediate-release products.

Now, as we're moving forward, a lot of the work that's going on in these guidances is much closer linked into the regulatory science

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activities where we need research in order to develop guidance on the more complex products. So this is a significant way that you see outcomes from the regulatory science program.

Just to give a sense of what I'm going to talk about, generic access in all the product categories -- we've tried to develop a research portfolio that's broad across a range of activities. So I'll talk today about complex active ingredients, topical dermatological products, inhalation products, ophthalmic products, nasal products, liposomes and nanomaterials, microsphere products.

As I mentioned, each of these is probably at least multi-billion dollar market of products without generic competition available because of some of these scientific challenges.

For the second topic on the confidence in generic drug substitution, I'll talk about our brand-to-generic switching studies in patients, which we have begun to present at scientific meetings, and really changing some of the debate

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about generic substitution; talk a little bit about post-market surveillance of generic substitution, and our product-specific standards.

In the tools for development and review, we'll talk about some of our modeling and simulation activities, but also the analytical and in vitro tools that help really develop more complex products. If you have an in vitro release test, that's something you can use to guide your development of a bioequivalent product, and many of our research projects are touching on that critical aspect of pharmaceutical development.

We have approximately 20 collaborations with different FDA labs on new analytical methods that impact some of our generic drug approvals. I'll talk a little bit more in specific examples as we move forward.

So focusing on the little bit deeper analysis, going through some of these product categories under generic access, one area of complex products are the complex active ingredients: peptides, complex mixtures, natural

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source products.

Under GDUFA, we've approved the first ANDA for glatiramer acetate generic. This is an immensely complex product. It wouldn't have been possible without significant scientific work from our scientists and our FDA lab collaborators to use high-resolution analytical methods to support the evaluation of those ANDAs. It's a critical approval, a multi-billion dollar drug product, many long, complex review processes. Without a strong scientific foundation, you'll never be able to approve products like that.

To move forward in other longstanding complex products, we have draft guidances under GDUFA for conjugated estrogens, a natural-source product that's challenged FDA for 20 years. And we have a guidance with extremely detailed information about analytical methods, developed in conjunction with our FDA laboratories in St. Louis, to provide a clear pathway for how to analyze these types of products. There's still a lot of work to do for the applicants to match up these complex products,

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but we've really provided, I think, a clear pathway for that in these guidances.

We have other draft guidances on other complex mixtures as well, so the sevelamer products, talking about characterization, natural source mixtures for the omega-3 products.

On our guidance agenda, we have on our public guidance agenda a guidance on rDNA origin reference products and the pathway for generic versions of those that we hope will be appearing sooner this year. But it's on our public agenda.

We've been able to clear the backlog on controlled correspondence questions related to this type of peptide sources. This is another complex category where access to generics was blocked in the past, but through the scientific efforts that we've made, we've been able to open up that pathway moving forward.

We still have research activities in this area. Many of these complex products raise issues related to impurities and immunogenicity. And we're working with many FDA internal collaborators

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to develop better tools for assessing that, for identifying if there are differences in impurities, whether they'll cause any risk or not.

We continue to work on the high-resolution analytics and multivariate data analysis with our FDA lab collaborators to develop the analytical tools that will help advance this area. But you can see here the huge impacts of a strong scientific foundation on pathways towards complex generics, and even approvals of very complex products.

The challenge here -- just this cartoon is, what you try to do in these analytical methods is you look at some of the pieces from your analytical methods, and through the combination of complex modeling and simulation approaches and the analytical methods, try to reconstruct similarity of the products. So there's a lot of complex science that goes on behind these approvals, and the resources from the GDUFA program really support that activity.

Probably the largest category where there's

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no generic competition are the inhalation products. And we have significant research activity here looking at the role of dissolution, particle size, PK studies. We have CFD modeling projects.

We have research that's supporting looking for areas where we can move away from having a requirement of being Q1/Q2 for the inhalation products to understand. For excipients that have been used in other inhalation products, they may be acceptable under certain conditions in identifying the analytical and in vivo studies that are needed to support that.

So there's constant research to advance our understanding of this product category, but we've been extremely successful in GDUFA at translating these research findings into guidances in this particular category.

So as of our April posting, we now have 13 product-specific guidances for inhalation products available. So when we started GDUFA we had none, no pathway for this I think multi-tens of billions of dollar a year market. No guidances at

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all. Right now we have 13 available for different product categories. So there's significant scientific activities that support this.

We recognize that these products and these -- what we're asking in the guidance is very challenging in some places, so we still have research activities to improve, identify better dissolution methods for inhalation products that may help you select particle -- raw material suppliers.

It may help us review that to look at alternatives to some of the very challenging studies that some of these guidances ask for. But we've made a huge effort in providing guidance across this very large and important product category.

Really, this pushes a lot of the responsibility onto the industry to engage with these guidances to develop products; if you have questions, to meet with us around this area. We've also had significant pre-ANDA meetings with companies working in this space, responding to

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these guidances, and we've prioritized those because this is a complex product category with essentially no generic competition.

In ophthalmic products, again, there's been very challenging generic products that require very difficult clinical endpoint studies in the past to develop. We've been developing guidances with alternatives to those, two guidances specifically under GDUFA for some of the ophthalmic emulsions that provide what we call a Q3 approach.

So this is having a formulation that has the same active and inactive ingredients, but also the same microstructure as well, as we've determined for these cases that that's the most appropriate bioequivalence method. It's much more sensitive and reproducible than a potential clinical endpoint bioequivalent study for those products.

We have a broad portfolio of research activities in the ophthalmic product space that includes modeling and simulation, but also significant efforts on in vitro release methods for ophthalmic suspensions, ophthalmic emulsions,

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ophthalmic ointments, to really broaden the ability to apply these Q3 approaches to other dosage forms as well. We've also done a significant amount of guidance development in this ophthalmic space. We've produced 10 guidances for ophthalmic suspensions.

We're engaged in research activity to improve ways to do some of the very difficult and challenging aqueous humor PK studies, and also the significant focus of research on the Q3 opportunities in this case, again, another large product category with very limited competition for the ophthalmic suspensions, ointments, and emulsion where there's been significant research activity, very significant guidances coming out that will enable competition in this area in the future.

In the nasal product category, we have research activities looking at the role of PK studies, in vitro and in vivo modeling projects. But I want to point out also one innovative technology, the MDRS particle sizing. This is Morphology-Directed Raman Spectroscopy. This is an

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instrument that wasn't even available until 2012, but it was used to support an ANDA approval in 2016.

So before this technology has even been used in a new drug application, they used it to support a generic drug application. And this essentially allows you to, if you have a suspension that has two different types of particular sizes, do a particle size comparison of only the API active ingredient. So this is critical for doing a Q3 analysis of some of the more complicated suspensions.

We wouldn't have been able to do this. We wouldn't have been able to approve this product, unless we had one of these pieces of equipment in our FDA lab to understand how it works to be able to give good responses to the submission to analyze them correctly. So without our investment in the regulatory science foundation, we wouldn't be able to approve these complex products through this type of pathway and using this type of very current new scientific technologies to support approvals of

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these complex products. And this is a category -- there weren't any generics in this space before this approval. It was supported by this novel technology.

Another product category where there's significant lack of generic competition is in the topical dermatological products. This is a little bit different. There, we have longstanding clinical endpoint studies in this area that have been used. So there are some generic products available. But if you look at the category -- and we have for the topical corticosteroids a pharmacodynamic endpoint approach available.

But compared to the broader population of products, there's still a large number of topical products that lack generic competition in this area. But it's a much broader number of products than a lot of the other complex products.

But we have a very significant coordinated research activity to advance the Q3 equivalence approaches for these products. We're collaborating with people round the world. In this project,

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we're working with people in Europe, Australia, and the US, generating new in vivo data. We're manufacturing semisolid formulations, characterizing them. We have modeling approaches integrated into this approach.

We've made significant progress in this area. We've done, as an example, some Q3 testing on some acyclovir creams. We've obtained formulations from around the world to look at them, characterize them through all of the different characterization methods are available through the rheology, the particle size characterization.

We've looked at them in in vitro permeation tests, which are excised human skin studies. We've looked at them through in vitro release tests, which are artificial membranes, putting together a full picture to understand which of these tests are appropriate for comparing formulation differences.

I think one of the things I'm most impressed with for the regulatory science program in the topical area is an in vivo study that we've done on what's called open flow microperfusions. This is a

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type of microdialysis. And we did a 20-person study looking at two different -- comparing the US reference product to a product that's available in Europe.

This study shows -- one of the challenges with the microdialysis studies in the past has been, are they reproducible? So this is a replicate design study. We show that using the reference product, you get very reproducible results.

Our investigator in this did something very novel. So essentially, all of the microdialysis in the skin data that's available in the past has been limited to about 6 hours because you had to hook people up to these giant pumps. They couldn't move, so they were stuck there.

New technology. These are wearable microdialysis devices. So people look like cyborgs in the pictures with them, but they can walk around. You can then get out to 40 hours of data, looking at the long time, so just basically the leading edge of approaches to this type of new in

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vivo study that is directly relevant to drug delivery across the skin, again, funded by -- and publication in this is under preparation. Should be available soon. We've talked about these results at public meetings as well.

We've shown that in a reasonably-sized study, 20 subjects, you can demonstrate bioequivalence between the replicate studies, and you can also show that a formulation that we know is Q3 different also has different drug delivery and doesn't show equivalence as well; so a strong development of a potential new in vivo approach to this as well as new characterization- based approaches.

We've also done work on looking at the IVPT and developing ways to do bioequivalence comparisons for these types of in vitro permeation tests as well that could be used for bioequivalence. But also, these studies are used right now in product development to select formulations and really help understand a lot of -- they're also used for post-approval changes

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as well, so having better ways to do statistical comparisons for them.

By lining these up with different formulations, we've been able to compare between different labs, different collaborators in different labs, to help us develop better protocols for how to do these in vitro permeation tests.

Another complex product category is the liposomes and nanomaterials -- seven grants on in vitro release, product characterization, identifying the critical manufacturing variables. We have guidances now on many different liposomal products under GDUFA guidance, on some of the nano-sized iron chelate products as well, to help develop generic versions in this complex product category.

We have a significant program in looking at some of the long-acting injectables and microsphere controlled-release products, nine grants looking at different aspects of these products. We've developed guidance on some of these products under GDUFA. I have some pictures here of some of the

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microspheres that we're doing.

Here we've also seen a significant interest in the number of pre-ANDA meetings. There seems to be a large interest in these product categories. They're very long-acting, so there could be challenges to do PK studies for long periods of time. So we're really focused on also the characterization of these materials as well.

So this is a significant area of very limited generic competition in this product category that we think that will be enabled, and will have a much stronger fundamental of the material science that drives drug release in these products from these research activities. And this will feed into our discussions with you in pre-ANDA meetings, our views of these products, and our development of guidances in this product category.

In looking at complex drug-device combinations, this includes the dry powder inhaler, the metered dose inhalers I mentioned earlier, nasal sprays, but also transdermal systems, auto-injectors. This is an important area for research

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to understand the patient factors that affect how people use devices.

This is something that's an emerging area for the review of these products and developing these products. How do you compare the devices? How similar do they have to be to be a substitutable generic product? What types of studies and comparisons of the device you have to use?

So a lot of our thinking of this is fed into our guidances on the metered dose and dry powder, especially the dry powder inhalers, where there's lots of diversity in the devices.

But also on our guidance agenda that will appear soon, there's a new guidance on adhesion for transdermal systems that's been developed as well that will be a transformation on how we do the adhesion bioequivalence studies. We have research activities looking at the irritation type studies for transdermal systems as well, as well as the patient use factors.

So again, significant efforts in trying to

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understand the regulatory review issues related to these more complex drug-device combination products that are eligible for generics can reference these products.

Another significant guidance that was developed is our guidance on generic abuse-deterrent formulations. This guidance, that was released in March as a draft, provides a path for generic versions of abuse-deterrent opioid formulations; relies primarily on a comparative in vitro and occasional PK studies. But the GDUFA research support was essential to this guidance, so this has a huge public health impact. It's a very controversial area. We have to have very strong scientific foundations for anything we do in this area.

We had a contract with NIPTE through our GDUFA regulatory science research to do external research on this, but also significant support for ORISE fellows in FDA's labs for testing these products. So without this recent GDUFA research, we wouldn't have that guidance. We wouldn't have

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that impact. We wouldn't have a pathway for generic versions of currently approved abuse-deterrent formulations.

I think this will be also an important part of FDA's overall view of the landscape of abuse-deterrent formulations. Once you have a pathway for generic versions, that gives people confidence that as products move towards abuse-deterrent formulations, there will be generic versions available in the future now that we have this guidance and a clear pathway for that. But without GDUFA regulatory science support, I don't think we'd be anywhere near this point without the data that we developed, both internally and externally, on this very complex issue.

Now, changing a little bit to talk about the confidence in generic drug substitution. So one of the things we've been doing in this area is brand-to-generic switching studies in patients. As many of you know, almost all generic products are approved based on studies in healthy subjects because we think that that's really the best test

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of the formulation comparison. So from a scientific point of view, we have strong reasons to understand that.

But sometimes, if you think from a clinical perspective, you say, well, these products are used by patients, and you're testing them in healthy subjects. Does that make sense? So we've worked in several areas where there's been significant questions about generic substitutions, specifically, first, for anti-epileptic drugs and immunosuppressant drugs, to do studies that look at generic substitution in patients.

Essentially, from FDA's point of view, we absolutely believe that these studies are going to show they're equivalent. We've really focused on what we think is the strongest, most sensitive test of the formulation. But this really helps the broader community understand generic drug substitutability.

So we've conducted these studies. We give an overview of what they look like. These are generally replicate studies where people go from

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the generic to the brand to the generic to the brand, back and forth. We generally look at PK outcomes, but we show very clearly -- this is the first study that was conducted at the University of Maryland with Jim Polli, who I think will be speaking later today, bioequivalence in generic and brand product, PK profiles essentially superimposable between the brand and generic.

We did a similar study with a different group, looking at generic-to-generic substitution; again, similar type of design, here looking at what they thought was the lowest generic versus the highest generic, trying to look at the extremes of the space, to get approved under our standards -- again, completely bioequivalent in patients in both of these cases. A similar type of study design in transplant patients on generic versions of tacrolimus; again, direct comparison in patient population bioequivalence as well.

So we've begun to publish these results. As we've published these papers, there's been accompanying comments or editorials about this.

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And I think this really shows the significance that this type of data can have on the community perception of these drugs.

Organizations that have been generally skeptical of generic substitution said these studies really are a step forward in addressing their concerns. We worked very closely with these communities to say, what kind of studies would address your concerns about generic substitution?

As we follow that up with the publication from the second study, again people have questioned the safety of generic substitution. Quite reassuring that organizations with a negative attitude to substitutions would consider reviewing their position. So I think these new sets of data are an important and critical part of understanding confidence in generic drug substitution.

It's a very different way to approach questions about generic substitutability, but it really -- these are the most expensive type of studies that we support under our GDUFA regulatory science program. So it requires significant

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resources to do these types of studies, and conduct them, and make them publicly available from that.

In this area we're also looking at -- the question is about substitutability, confidence in generic substitution. So we've also funded research to help us get an idea about what are the patient perceptions about generic drugs? What are physician perceptions about that? So we've published some of this work as well to understand what drives questions about generic substitutability, both in patients who generally prefer generic products and also physicians confidence in this.

But again, I think we've seen that -- our collaborators on this saw an increase in confidence in generic drug substitution over the last few years. And I think it's very useful to see that, but this is a way to measure broadly how we're doing as an industry and a generic drug program in reaching out to both patients and physicians about generic drug substitutability. So this has been part of our generic drug research program, to

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provide this baseline information, as well.

Other aspects of confidence in generic substitution have to do with making sure that we are monitoring the products that we approve effectively. And there's really two large sets of data that you could potentially look at to say, are generic products being substituted effectively?

So we look at adverse event reports. These have very significant challenges for using them to look at generic drug substitution. Oftentimes people don't know which generic product they're taking. There's huge potential reporting biases. I've been switched to a generic. Am I more likely to complain about something that just was a normal expected adverse event from the brand product? Questions about normalization.

We have some research activities looking at authorized generics. So these are generic products that are essentially the exact product as the brand product, just marketed differently, to see what types of adverse events people report about those products. We do actually see complaints about

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generic substitution with authorized generics. So that's an interesting, unique, natural experiment to help understand some of the biases in figuring out what's really significant.

The other big chunk of data that you could look at are either electronic healthcare records or insurance claim data. These have some advantages. They oftentimes can be linked into an NDC code to a specific product. But you may see substitution events here.

But there are significant challenges with how to look at this data to understand questions about generic drug substitution. So we have some research activities to look at substitution patterns -- what do you expect to see? What would be unusual? Looking at how to compare other things.

But I think in the future, these datasets are going to become more -- we're moving toward a big data future. So these datasets are going to be available to more and more researchers, more and more generic companies. So we have to be prepared

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to think about how we're going to analyze generic substitution questions in these types of information sets and do it in a way that gives us good information.

I think there's lots of ways in these retrospective datasets to do bad studies, and that can give misleading results about generic products. So it's really important that we have a broad-based research program in understanding how to do these types of analysis well for these specific questions about generic drug substitution.

The other side of confidence in generic drug substitution is making sure that people have confidence in the standards that we as FDA are applying to products. And two areas that we focused research efforts on are for narrow therapeutic index drugs.

So we're really moved significantly, under the first few years of GDUFA, to providing guidances identifying which products we think have a narrow therapeutic index, and having tighter bioequivalence standards on that.

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We think that sort of risk-based standard, the idea that there's higher- and lower- risk drugs and they should have tighter standards for the higher-risk products, I think is a strong part of confidence. I think there's been -- there's some challenges as we change guidances and evolve our standards in this area. But this is moving toward, I think, a much stronger foundation for our program. As we get ahead in guidance development, we should be making these decisions on which drug we think have a narrow therapeutic index very soon after the new drug approval.

We have a new internal working group to coordinate activities between OGD, OCP, OND around which drugs have a narrow therapeutic index. So what you can expect to see in the future is these decisions made much earlier, before any kind of generic drug development happens.

Similar thing with a partial AUC. This is an approach to say, there's a smaller number of products that may have very critical -- the PK profiles being much more similar than needed. And

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we work closely to develop those cases. And again, as we move our guidance development closer to the new drug approval, we want to have these questions identified early.

So this links into the tools for development. Both of these examples -- narrow therapeutic index drugs, partial AUC comparisons -- really are driven by what I call the pharmacometrics for generics. This is the PK/PD response.

Which drugs have a sharp exposure-response relationship? Which drugs have a close connection between the shape of the PK profile and their pharmacodynamic responses? This is a scientific question that's going to determine whether we have tighter standards for these two categories.

So we're trying to support strong program internally and through research in what I call the pharmacometrics for generic drugs. This is the PK/PD modeling that can support these risk-based decisions, provide the input into this. And these two critical questions are the most important

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applications of that, and they drive our guidance development and our reviews of the activities. But I think as we establish a clear scientific foundation, it will also be clear to the industry, as we develop the products, which cases this is important.

The other modeling and simulation area that's critical, links into the complex products, is that we have a broad set of what we call PBPK for non-oral routes of delivery. So we had a workshop yesterday all day on solid oral dosage forms. That's much more well-established science of absorption modeling than the non-oral routes.

But as we look at the landscape of complex products, it's the non-oral, the ophthalmic, inhalation, nasal, topical products where much of our activity and our scientific challenges are going to be found.

So we want to have a strong mechanistic foundation of drug absorption on all of those categories. So we've begun to fund, in each of the categories, several research activities to begin to

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advance the models that are used for drug absorption through these routes of administration. And this, I think, will serve as a scientific foundation for our program going forward.

The third aspect of the better tools -- and this links a little bit closer to product development -- better in vitro release methods. We know that generic drug development strongly depends on having good in vitro release methods to pick your formulation, to determine which product you're going to put into your bioequivalence studies. So we have significant research support in the solid oral dosage forms. This links into the oral absorption models.

Some of the research we've been funding in this area are direct measurements of GI concentration of drug. This is the thing that sits in between. I do an in vitro dissolution experiment. I give the product to a patient and measure some PK profiles. But what's really the mystery is, what's the in vivo dissolution of the product? What happens to that drug product in the

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GI tract?

We can try to infer it from what we test in the lab, what we measure in the PK profiles. But to really be sure we're doing it correctly, you need some direct measurements of what's going on in the GI tract. So we've done intubation studies to measure that directly to provide a unique, albeit limited and highly expensive to obtain, dataset that can really help drive better in vitro release methods for solid oral dosage forms.

But for the complex and locally-acting drugs, here it's much more of a challenge. For each product there may be a specific type of in vitro release test, but probably 20 of our grants have outcomes of improved drug release methods for these complex or locally-acting products.

This touches on the in vitro permeation and in vitro release tests for the topical products, for the ophthalmic products, identifying for the different suspensions in ointments. What's an appropriate dissolution method that will help us

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evaluate product equivalence and help develop bioequivalent products? So these in vitro tests are critical in these complex product areas.

We have some for the inhalation products on dissolution. I think we've received very significant feedback from people informally that these are critically important to the development of some of the inhalation products.

People have approached our collaborators. They're trying to buy the method and buy them out. So I'm glad we funded it and make it publicly available to get these into the public domain. So there's a lot of interest in the dissolution methods for the inhalation products as being critical to product development as well.

So again, what we're interested in today is your input into these areas. So as you talk and you hear questions from us, we're probably going to ask you, how does what you're proposing help provide generic access across these product categories, or build confidence in generic drug substitution, or provide tools for generic drug

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development? So we want to develop our future agenda in these types of categories. So I'll try to fit our questions and inputs into your discussion as we have the discussion going forward.

But just to conclude my initial discussion, there's a huge public health impact for a relatively small regulatory science investment. All right? My return on investment calculation says that if we approve generics in even one of these categories, that's a multi-billion dollar a year benefit for a program whose net cost over five years is around $100 million. So just one of these product categories can give you 100-fold return on investment. And there's multiple multi-billion dollar categories that are being addressed by this.

This broadly puts a strong scientific foundation for our program; that's of huge benefit to the industry and to the public. We've taken these research activities. We're driving guidance development for complex products. The inhalation guidance, I think, is the leading edge. That's the one we've recognized for a long time is the most

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significant one.

You see there, as these research projects drive in, you see this surge of guidances across that product category, 13 in that specific category alone, enabling broad generic competition in a very complex product space.

A lot of these issues are very complicated, not just externally but also internally. We have to get alignment across -- in order to have a guidance on abuse-deterrent formulations or adhesion or rDNA source RLDs for peptides, there's a huge number of internal stakeholders have to get aligned on that.

The FDA research activities in there can be very critical in driving that. They provide data that people can look at and say, well -- people can raise hypothetical concerns. We have real data to address that. We can help drive the alignment on getting a policy or guidance implementation of these complex issues out. So there's lots of things going on behind the scenes on many of these complex issues that are in addition to the publicly

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available science.

The confidence. I think the FDA scientific support for confidence in generic substitution is very unique. Even if a generic company went out and did these studies on generic substitution, right, they'll say, well, you have an interest and a bias in that.

I think when FDA supports them, when we partner with academic groups that are essentially -- and some, in some cases, have been skeptical of generic substitution in the past. I think that makes a much, much stronger public statement of confidence in generic products that really has the biggest possibility for impact on perhaps even changing some of these groups that say, don't substitute approved generic products.

I think, from FDA's point of view, we wouldn't approve the products if we didn't think they were substitutable. And we hope that people will begin to understand that and see that perspective. But this type of data really provides very strong prospective studies designed to answer

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those questions and prove that.

The tools that we're developing -- the goal is faster development and review. If you have right modeling and simulation tools to predict what's going to happen in the bioequivalence study, if you have the right in vitro characterizations to say, what's the critical attribute of the brand product and does my product match that, that's going to drive faster product development.

But that's also going to drive a faster review. If you have strong tools that say, this is the right study, this is the right analytical data, we'll be able to make better decisions and evaluations about that. And by having these tools publicly available, everybody knows what they are. They become commonly established. That feeds into this cycle.

I think, from my perspective, it's been incredibly exciting to be involved in the growth of this part of the generic drug program. And the input that we get from these public meetings and the comments to the docket really help align what

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we're doing with what the needs of the industry and the public are.

I really personally appreciate all of the comments that you've given. And I think it's just incredibly exciting to be involved in all of these different research activities across FDA with all of our external collaborators.

So with that, we will be moving on to our first speaker of the day, and I have to go back to my seat so I can change roles. So our first speaker will be Dr. Michael Fischer from Brigham and Women's Hospital, Harvard Medical School, to talk about regulatory science for generic drugs. So welcome.

Presentation – Michael Fischer

DR. FISCHER: Great. Thank you very much. Thanks for the introduction and for the opportunity to speak here. As Dr. Lionberger said, my name is Mike Fischer. I'm a primary care physician and a researcher in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital, affiliated with Harvard med school. I'm

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presenting on behalf of a group of several of us in our division who do work in this area.

Dr. Lionberger was kind enough to cite a couple of the projects we have ongoing, and it's a nice chance to thank the office for the chance to collaborate on that initial work. And what I'll be doing is making some suggestions on what those of us in our group working on this see as exciting new areas to move into in the coming months, years, and into the future.

Since it's in the printed materials, I won't read what's on this disclosure slide in terms of potential conflicts of interest. It's all there printed for those as needed.

Quick orientation on what our division is. The Division of Pharmacoepidemiology and Pharmacoeconomics, besides having large business cards -- although I think the FDA has equivalently long titles for their offices, so I feel much more at home here -- we're a group of 18 faculty members. We mix health services research, drug safety and outcomes research, a lot of methods

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work, law and policy.

We have a diverse portfolio of funding -- as I mentioned and as Dr. Lionberger cited, some work with the FDA, but also grants from many federal and federally affiliated agencies, as well as a variety of collaborations with manufacturers, with insurers, and with others.

We have several specific programs. I direct the National Resource Center for Academic Detailing, which is supported by AHRQ and does direct outreach to front line clinicians. Aaron Kesselheim, who testified at this meeting last year, runs something called PORTAL, the Program on Regulation, Therapeutics and the Law, that looks at regulatory science. Our colleague, Niteesh Choudhry, runs the Center for Healthcare Delivery Sciences. And then we have other core faculty who have various roles at PCORI, FDA, Sentinel, and others.

So that's who we are. Let me transition now to what we want to put forward as suggestions. And the format for the several slides I'll have, just

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since we used the same format for all of them, is basically we'll cite a piece of existing evidence to set the stage. I'll be hitting those very briefly, just given the time constraints that we have.

Then a couple -- one or two research questions that we would suggest for the coming months and years. And then a quick note about why we think that's relevant for this office, what the results of that sort of research might offer as useful information.

So the first area are single- or limited-source generic products. This is a paper that's currently under review out of our group. But over a third of the entities eligible for generic competition have three or fewer approved generics. And as I think lots of people in this room would know, many are single source.

So from a research point of view, trying to get a better understanding of the predictors of when a generic agent will become available only from a single source would be a productive area for

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study.
From a regulatory point of view, being able to identify proactively, prospectively, when that situation may arise and sort out what might be appropriate targets, either for regulatory or incentive-based approaches when these situations are coming up, might help address that problem.
Similarly, thinking about the next stage in that cascade, how does a single-source generic change utilization patterns or clinical outcomes when compared to multi-source generic medications?
Understanding the impacts of, especially single-source generics, again would provide useful information for FDA regarding the impact of policies that might be considered, or eventually implemented, to address the challenge of single-source generics.
The next topic we wanted to put forward for consideration is generic medication shortages. There, I think again, the background would be familiar to most of the people listening to this session. Over the last six years, over a thousand

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drug shortages were reported to the FDA. So there are several research questions that we thought would be of interest in this area.
When these generic drug shortages arise, how do prescribers and other clinicians change their treatment patterns in response to generic shortages? Both what are the changes in prescribing patterns or, looking at clinicians more broadly, in other ancillary care delivered? What are the spillover effects when there might be a generic shortage?
Our group is especially interested in medication adherence. We do a lot of research on chronically taken medications. So when there are generic drug shortages, what are both the immediate and the longer-term effects on patient medication adherence? And do those changes, most importantly from a patient-centered point of view, eventually affect clinical outcomes?
All of these findings at the different stages in the process might allow for contingency planning in the event of future medication

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shortages which, based on experience, seem like they will continue to arise.
Generic drug safety and effectiveness of course is of huge interest to this office, and as a broad topic, the areas in which our division has had interest and that we'd put forward for consideration here. Drug recalls are of course common, occurring nearly once per month.
So one of the interesting questions to look at is whether there are specific manufacturer characteristics or other characteristics to help predict which generic medications are most likely to have safety -- that should be "or," not "of" -- to have safety or effectiveness problems when they're on the market.
Related to that is the increasing use of compounded drugs as well. So we'd be interested in research on the question of whether compounded generic medications differ in their safety and effectiveness from other generics. Findings from both of these areas could help provide guidance for regulatory policies or safety interventions with

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clinicians or with manufacturers.
This is some of the research that Dr. Lionberger cited that our group's been very interested in, looking at patient and clinician attitudes, beliefs, and behaviors regarding generic drugs. We've done studies, going back several years, finding that patients and prescribers have some degree of skepticism of generic drugs, although that has been changing over time.
One of the areas that we think is interesting, and the kinds of research that we do and the kinds of large datasets to which we have access, are those prescriptions that are written, "Dispense as written," which is often either written by the prescriber or elected by the patient, both of which indicate some degree of skepticism about generic drugs.
Identifying prescriber or patient characteristics that predict that decision can help identify areas for educational interventions when that's an avenue that can be used to increase the use of generic drugs.

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Another policy area of interest is the increasing frequency of drug coupons used for hundreds of agents, often those which do have generic alternatives available within their therapeutic class, if not a direct generic substitution.

So an interesting research area we'd put forward would be understanding how the use of drug coupons changes the rate of prescribing and dispensing of generic medications, both in terms of initially dispensed prescriptions; but especially, thinking back to the point I raised a slide or two ago when I talked about shortages, thinking to longer-term medication adherence and patients' persistence on medications that are meant to be taken chronically could inform the policy debate on coupons and how they should be regulated.

Then, as I've gotten the two-minute warning and needs to start throwing passes close the sideline, I'll come to the last one of the topics that we'd put forward before I sum up -- is just thinking more broadly about the clinical importance

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of these generic medications; thinking about, in light of a study from Josh Gagne in our group that came out a couple of years ago showing that patients getting generic statins had better initial and longer-term adherence, and actually better clinical outcomes due to more days on the medications.

That was an important study for thinking about this as not just a cost and adherence issue, which in the end are intermediate outcomes, but really a true hard clinical outcomes topic.

So understanding whether patient outcomes differ based on the use of generic versus branded medications across a wider range of therapeutic classes can provide critical information for clinicians, for patients, for payers, for regulators, for everybody in this space who's making decisions about treatment and coverage.

This summary slide just simply relists the research opportunities that those of us in our research division who work in this area, and who've been excited so far to work with this office on a

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few of the projects that Dr. Lionberger cited, would be excited to see coming in the months and years to come:

The predictors and impact of single-source generics; the impact of generic shortages on use and outcomes; the potential predictors of recalls or other safety issues; the safety and effectiveness of compounded generic medications; predictors of "dispense as written," the impact of drug coupons on generic use; and the clinical outcomes of generic versus branded medications use across a range of therapeutic classes.

So with that, thanks again very much to the office for the opportunity to present, and I'm certainly happy to engage in questions or discussion if that's helpful.

DR. UHL: I said to Rob, I have a question, of course. Thank you very much for your presentation. I really appreciate you coming here and presenting.

So if you back up one slide. Is that feasible?

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DR. FISCHER: I have the technology.

DR. UHL: You have seven potential research opportunities for us.

DR. FISCHER: Yes.

DR. UHL: We have, as Rob Lionberger just presented, approximately $20 million on an annual basis, which probably wouldn't cover all of those in any given year. So, and I actually ask this of all the presenters, if you can think about what Dr. Lionberger said about access across product categories, confidence in substitution, and better tools, can you prioritize that and give us what might be the number one priority from your list?

DR. FISCHER: Sure. This is a -- I'm smiling a little bit because there's a group of us who work on this, and each of us has the ones that we favor more.

DR. UHL: Of course they do. Of course you do. That's how this lays out.

DR. FISCHER: That's right. But this is what I get for being the one who is willing to come to Washington, so I get to --

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(Laughter.)
DR. UHL: We appreciate that. Thank you.
DR. FISCHER: Yes. So one quick note is actually -- and Dr. Lionberger talked about the sorts of data that are available. I'd put out there the point that our research group, as do several others, has a lot of data resources, existing resources with large claims datasets and so on, which actually can be leveraged. So a lot of the research can be done relatively efficiently in terms of the cost of doing research.
So I think, while I will actually answer your question and not dodge it, they can be done efficiently by our group and others, taking very sincerely your point that it is possible to do bad research with these observational databases, and one needs to be very careful.
That said, let me actually answer the question. I think among these, we would think about the ones that have the largest impact on hard clinical outcomes as being the most important. So I guess I can't really use -- well pointing at my

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slide doesn't do you much good. But I think about the impact of shortages on use and outcomes is an area where there has been a lot of concern, and that appears that it will continue to be a potential safety issue in the future.
The clinical outcomes across a range of therapeutic classes at the end, again very influential, both because it touches on hard clinical outcomes and because I think it will influence clinical guidelines, some of the pieces that Dr. Lionberger was talking at the end about clinical societies.
Then if I was going to just go with the top three for those, I think the single-source generics, which relates to the shortages, is another that we're very interested in, although obviously we're interested in all of them over the long term.
DR. TOUFANIAN: Thank you for your presentation. And following up on your last bullet, could you provide a little bit more information in the desired evaluation? Are you

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finding value in us surveying a range of therapeutic classes in order to assess the generic space entirely? Or have you all identified specific therapeutic classes for which you'd like additional evaluation?
DR. FISCHER: So in that last bullet, I think, as an academic group, we're interested in all of them. The study I cited looked at statins and cardiovascular disease. And I think realistically we would anticipate -- for the kind of research that we do, so other groups may speak to different sort of types of designs -- we would be looking at highly prevalent conditions where you have a lot of patients who are treated with both generic and branded medications.
So it's spaces like outcomes of diabetic care, anti-hypertensive treatment, medication classes where there are a large number of patients under treatment with both branded and generic agents, and relatively higher risks of adverse clinical outcomes. So those are the ones we would start with.

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If you asked us the long-term question, eventually we'll study everything and then when we've studied all the drug classes, we can all retire.
UNIDENTIFIED SPEAKER: (Comment off mic.)
DR. FISCHER: That's a good plan.
DR. LIONBERGER: All right. Thank you very much.
DR. FISCHER: All right. Thank you.
(Applause.)
DR. LIONBERGER: So our next speaker is Professor Gordon Amidon from the University of Michigan. He'll be talking about regulatory product research.
Presentation – Gordon Amidon
DR. AMIDON: Thank you, Bob. I'm going to talk mostly about oral products, the biggest product category that the FDA has to deal with in the generic area. And I'm going to talk about product research, not drug research. The patient gets a product, not a drug. We all know that, but we use the term drug when we mean product. So I'm

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going to talk about product research, if I can do this. Okay.

So I'm going to argue that the bioequivalence needs some scientific development, which is happening now today for the first time. We need things such as Cmax predictors, AUC predictors. Remember, bioequivalence is about the same drug, different products. Same PK. Same ADME -- same DME, I'm sorry -- different absorption. So the science of bioequivalence is at the absorption site. And we need to extend in my area, oral, to further immediate-release and modified-release oral dosage forms.

The BCS that started this, I'm going to say 20, 25 years ago, was actually funded by the FDA 25 years ago, when Carl Peck was the Center Director here. And that's really been penetrating further and further. And today I'm going to propose we do subclassification, the next step, I think, in biopharmaceutics classification.

My thinking when I was working with the FDA in 1990 -- on sabbatical; they let me out after one

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year -- was, some products are simple. Some are hard. Why? Why? So that led to eventually categorizing in a classification system.

We now have guidances based on BCS which allow in vitro biowaivers for BCS Class I drugs, I think probably principally based because if drug products dissolve rapidly in the stomach -- disintegrate, dissolve rapidly -- what you're measuring in vivo is gastric emptying, not a product difference. So why do it?

So at any rate, we're continuing to pursue that line of reasoning and how far we can develop the dissolution methodology to Class III drugs, II and IV low solubility drugs, and then modified release products, which are even more complicated because of the changing luminal environment along the intestine, as well as the differentiation of intestinal cells along the gastrointestinal tract. So we continue to do studies there.

I think the key science then for oral delivery, oral product equivalence, is in vivo dissolution, and I think Dr. Lionberger mentioned

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that earlier. What's really happening in the gastrointestinal tract? Surprisingly, we really don't have much measurements there, especially under dosing conditions or our standard bioequivalence conditions. So we need to look at the media and methods.

I'm going to propose an in vitro -- I'm sorry -- in vivo predictive method, dissolution method, which is not a QC method. That's a separate science, so that's -- they do a good job over there for quality control. That's a whole package for a product. But for product development we need a dissolution methodology and that would be useful for things like SUPAC changes, scale-up post-approval changes, dose scaling, biowaivers, even QbD and PAT targets for modification of manufacturing process.

What's your target going to be? Clinical? Human? No. Way too expensive. We need a better target, and that would be the in vitro dissolution for oral products if we had confidence in the dissolution methodology as representing the in vivo

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processes.

So that's what we're in the process of trying to do at Michigan with various intubation. I think, again, Dr. Lionberger mentioned this as one of the FDA contracts where we put a tube here. In human subjects we measure 15 motility -- contraction; pressure contractions; different sites, stomach, duodenum, jejunum, ilium; as well as sample from those four sites.

We aspirate fluid and assay for drug marker pH, buffer capacity. It turns out buffer capacity is way much lower than the USP buffer capacity. I'm not even sure why we call it simulated intestinal fluid because it's not. But we're learning things like that, and we're measuring drug concentration in the intestine.

So we're learning now for the first time what's really going on between the in vitro product you're developing, the manufactured product, and what happens when you put it into the human subject. We need something in between there. We don't want to use the human subject as our

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experimental apparatus. Right? We think we can do better. I know we can do better. So that's the whole process at Michigan.

So we're measuring gastrointestinal variables during drug absorption, gastric emptying, duodenal appearance, intestinal transit, various motility, pH buffer, physical-chemical changes.

One element that we finished in the MRI, magnetic resonance imaging, to the gastrointestinal tract, we measured fluid volumes. It's not 900 mL, which we use in the USP for the apparatus. In fact, when we give a glass of water, that's all we see in the stomach, and then it decreases from there.

In the intestine, total intestine, we see on average around 70 to 80 mLs, total volume in the intestine, liquid volume. So how do we develop an in vitro apparatus? Well, that's what we're in the process of trying to do.

One point here. Here's the USP dissolution apparatus methodology for an RLD product, 100 percent in 15 minutes, 50 millimolar phosphate.

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That's a USP apparatus. But when you actually use something that's more physiological -- I'm not going to make a case that this is, yet, because we don't have the data -- but it takes 60 minutes to dissolve in a physiological buffer. Well, how do we develop a methodology that is reflective to in vivo? Well, we have to go after the in vivo data under relevant oral product disintegration.

So I'm proposing BCS subclasses. I'm not going into that in detail. But I think we need a product development person. If the drug is an acid, base, or neutral, that makes all the difference in the world to what you can do with it. So I think we need to classify dissolution methodology, what I'm calling in vivo predictive dissolution methodology, based on subclasses. And we're going to have a number of -- maybe 10 or 20 different, maybe more -- dissolution methodologies that would be predictive.

They're not going to be quality control, although quality control could be a derivative. That is, once you decide what's most important for

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your product, you could set a quality control standard. But what we need is a method to help us decide what is that critical variable, or critical variables, and then what standard do we set to ensure that product quality, over time, for both brand and generics. It's a product standard, not a drug standard. I mean, the drug is obviously critical, but it's a product standard.

So the in vivo test is our gold standard, no question about that. There's no argument there. We may have to tighten it for narrow therapeutic index drugs, but I believe that we need to develop -- and is the in vivo test the best? In some cases, we know it's not. For BCS Class I rapidly dissolving, it's not the best test because the in vivo test tells us nothing. Okay?

So how do we develop a predictive test? That's what we're in the process of doing at Michigan now, what I'm calling iPD. In vivo measurements under typical BE conditions are clearly needed, which is what we're doing. And then we can extend the GI measurements based on

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non-invasive MRI methods.

That's what we're currently implementing -- developing the protocols to do next year, collaborating with the world's expert group at measuring, by MRI, GI fluids and motility where we can do it in patients. We can do it in pediatrics. We can do it in special populations. So I think we're looking at how we extend these techniques to patient conditions.

So I think advancing product research in the 21st century is a bigger point that I want to make, is that for oral we need, of course, in vivo predictive dissolution methodology. And we need to measure the GI variables.

But when you think about the type of products and the list of topics and complex products, the topics that Dr. Lionberger referred to this morning were impressive. The range of issues the FDA has to deal with is enormous, just enormous.

I think it's maybe incomprehensible to most of us how many different things, and the expertise

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you need to develop a good scientific decision around the world.

So I think we need, really, a product regulatory research institute. This is blue sky, of course, but what do we need to regulate products for the 21st century when we're seeing all of these complex products come down the pipe? And where do we get the expertise to make the best decision we can make on that product for ensuring efficacy, to the best of our ability, to patients?

I think I finished on time. Thank you.

DR. LIONBERGER: So I have a question. If you could only get one -- so in the next year one new in vivo dataset to help advance in vitro predictive dissolution, what would it be?

DR. AMIDON: If I could only get one? Probably MRI.

DR. CONNER: Like yesterday and today, you've made some side comments as you were presenting your predictive methods, several times saying, oh, well, quality control measures, they don't really need to do this. The FDA --

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DR. AMIDON: Be careful. What I use -- okay.

DR. CONNER: I'm just interpreting what you say. You can correct me.

DR. AMIDON: I don't want to take down quality control.

DR. CONNER: The FDA right now is putting in quite a lot of effort to make their specifications more clinically relevant.

DR. AMIDON: Yes. Yes.

DR. CONNER: So wouldn't that effort dovetail with what you're saying, if making all in vitro -- or making relevant in vitro methods that predict what we want to know, which is usually relevant to the patients? So that includes both bioequivalence or bioavailability plus quality control, so that you have a spec that actually means something to the patient and to the prescriber.

DR. AMIDON: Yes.

DR. CONNER: It's not really that, oh well, it's no good for predicting what's really going to

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happen in people, but it's good enough for quality control.

You can correct me if I interpreted what you said is wrong.

DR. AMIDON: No, industry is working on that. Greg Amidon and myself, we were at a conference at Lilly three weeks ago on this particular issue. Lilly, Boehringer Ingelheim, Merck were there, and AbbVie.

So yes. It is happening in industry, but of course that tends to be private and proprietary. So how do we set public standards and to have that information in public so that it gets an appropriate vetting? But the answer is yes It's happening.

What we're developing is based on what was developed in industry. It's called the artificial stomach duodenum, ASD. I said to the inventor of this technology, you don't want to take something artificial to your boss, do you, unless it's a Christmas present or something. But at any rate, yes, so it's happening, Dale, but it's a matter of

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the public standards.

DR. LIONBERGER: Thank you very much.

DR. AMIDON: Okay, thank you.

(Applause.)

DR. LIONBERGER: So we will go to our break now, and we will reconvene about 10:40.

(Whereupon, at 10:22 a.m., a recess was taken.)

DR. LIONBERGER: Welcome back, everyone. I just want to let everyone know, we've had some questions. The slide presentations will be available on the regulatory science webpage as soon as possible. We will ask the speakers for permission before we post them, however, but we will have those that we have permissions available as soon as possible.

So again, to continue with our program, our next speaker is Professor Duxin Sun from the University of Michigan. So welcome, Duxin.

Presentation – Duxin Sun

DR. SUN: Thank you very much for the opportunity of presenting. This represents a group

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effort from the University of Michigan. So I will focus on the BE standard mainly for modified-release drug product.

So the current BE standard for IR, so immediate drug release product, works pretty good. I think mostly work fine. And the challenge is for the BE study of modified release and a locally acting drug product.

So of course we still use AUC and a Cmax comparison, and that's perhaps not enough. Then for some of the products we use partial AUC to improve the standard. That's definitely improvement, but still I think there's still challenge. I'll show you some of the data what I mean.

So I will present two ideas. One is one specific idea to ask, can we add this another parameter to compare the BE of generic and brand? And also then I also going to present, once we get the data, what are the broader implication?

So the question for this specific one is then I want to introduce this composite appearance

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rate. I show the later the data. What do I mean? The question is, how do we estimate that? How do we validate that? How do we compare between generic and brand?

So in the BE study, we use AUC and Cmax comparison. In here we use a simple -- the underlying assumption uses simple pharmacokinetics. So we made a pretty good assumption the absorption rate -- the absorption is the first order kinetics. KA is a first order absorption rate constant, is a constant. We know this is not right and yet we teach students all the time, for the last 30 years, because -- that's not because we teach students the wrong thing, because we have to make simplification.

For some cases, it does work. For example, in the oral dissolution case, that's perfectly work fine. For most immediate=release drug products, if they are really released, they have dissolution completed within 30 minutes. They're very similar, like a solution go down the GI tract. That's also works fine.

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The problem is for local-acting and modified drug release. So here what I mean is, you can see this slide is a busy slide. If you have MR product and local-acting drug product, they may or may not have a dissolution in the stomach.

Of course, they have structural gastric emptying. Then you go to GI small intestine. They also have dissolution release in different region of the small intestine differently. Of course, you have a transit.

Then some of the drug may have a precipitation, and then only the drug dissolving solution, they are absorbed through the membrane. So that's we refer to the first order drug absorption. Even that perhaps is not first order. I think along the GI tract, they may not be a first order.

So what I propose to you is another term; we can use deconvolution, get a composite appearance rate. Basically, use how fast drug can appear in the blood, then you can include everything here. You can include the drug release and the

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dissolution in GI tract, precipitation, perhaps even transit. So I show you how we did it, some preliminary data.

The question is specifically as applies to BE, then how do we exactly estimate that? How do we validate? How do we compare? So what we really need to do -- the last slide, I will show you what my proposal is. Here just refresh, is we really need to measure in vivo drug dissolution and releasing in human GI tract. So we have done, just finished the local acting drug product, and we are currently doing IR drug product.

We really need a one right now is modified-release drug product for in vivo GI tract drug release and dissolution. After we get this, we can get deconvolution from the plasma profile, get this composite appearance rate based on the plasma profile compared to oral solution. Then we need to validating statistical analysis to compare brand and the generic.

So I'll show you some of the preliminary data what do I mean. So in Michigan, we have this

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technology. We did 60, about almost 100 patient already for the intubation study. We put a tube in the human GI tract all the way down from stomach, duodenum, jejunum, and early ileum. So we cannot get colon because that's too down there.

Then you can see the different product in the different location. We get a sample from different location. We get a GI motility. We get a pH. We get a structural capacity. Then got really covered everything together.

I'll show you one piece of the data here to illustrate my point. So for example, we actually get a sample. The patient stays there for overnight but we can do intubation for 7 hours, so every hour we can get a sample. Then we measure drug concentration to represent the release and the dissolution in the GI tract. So you can see we did Pentasa, Apriso, and Lialda.

So here's the stomach on the very first left column, and from stomach, duodenum, proximal jejunum, middle jejunum, distal jejunum, and early ileum. So you can see from here Pentasa is

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released from stomach pretty high level and all the way from duodenum to early ileum.

Once the surprise is found in here, we never imagine -- we could actually -- by many years we can never imagine that the drug concentration stay in stomach for 7 hours. We always assume they finish by 2 hours or 30 minutes. Simply is not true, and we use that assumption for the last -- I don't know how long, 50 years.

So then what does that mean? What impact does that have? So that's very surprising. So you can see this drug release very clear, very beginning. They release from the very beginning to the end.

Now, if you compare Apriso, they don't have a release in the stomach. They have a very tiny small amount of release from duodenum to jejunum, then maybe start releasing in late jejunum or early ileum. That's a very clear difference between these two drugs, drug product.

If you compare to Lialda, Lialda is designed to releasing then later, the colon region of the

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intestine, but the scale is different. They almost have zero release, tiny, tiny amount of release, in early stomach, duodenum, jejunum, ileum. So you can see they are very different.

So of course then we also get -- for this study, we also get a plasma concentration. We also got an oral solution as another arm so we can compare it to. You can see here the top panel, the plasma profile Pentasa appraisal. Although I show you early slide, the GI release is very different.

Their plasma profile, there's some difference, but if you do it really well, you can make it bioequivalent based on the plasma profile. Of course, Lialda is designed differently. They are very different. You can see the plasma profile is very different.

So the argument I have is, the plasma profile cannot tell the difference in terms of GI release, especially for local-acting drug and for modified-release drug. However, if you do a deconvolution to gather this CAR, composite appearance rate, and the bottom rule, you can

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clearly see they are different.

Pentasa in the left lower corner, you can see release drug from the very beginning all the way until 10 hours. Then for Apriso, the first 3 hours there's no release, then sharp release, then perhaps stop release at 10 hours. Then Lialda is continued release later part.

So those slides tell you two things. One, the CAR is much more sensitive. We can mirror the GI real release compared to plasma profile. That's number 1. Number 2, very surprisingly, everything seems to stops around the 10 hours. So I'll show in other datasets. We don't know what that means, but maybe it means two things.

Number one, for modified-release formulation, maybe if you make too long after 10 hours, they are never going to be released because they reach colon. Colon have no water. Then they don't release. They don't release. They don't have no absorption. So that's one possibility.

Number two, so whether it's a release

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problem or absorption problem, my guess is perhaps release problem. So then does that mean in the future we should not make an extended release more than 10 hours? I don't know. If that's true, that has a vague implication.

So I'll give you another dataset. Here we use 6-week crossover, 6 different formulation, modified release drug in human. You can see plasma profile, 2 SR, 2 ER, it's similar. However, again, the CAR can tell clearly the difference and the release difference in the three different formulations. Again, the two points I showed last slides, these slides also confirmed.

So I think based on those preliminary data, my proposal would be we don't have any data currently for modified release drug product in GI drug dissolution, the release. We have zero. And we did get the locally-acting drug product. We will publish that in the next few months.

The ongoing studies for IR drug product, GI drug dissolution, so we want to get that. We hope to get another, at a minimum, MR drug release

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product. And also then we can estimate and validate the CAR compared with oral solution, then validate that by oral GI drug concentration. Then we need to statistically validate how do you compare this to a product. How do you use number?

So that's just a specific question. So once we get those data, then the broader implication will be we can validate the in vivo predictive dissolution condition, device, everything, and also validate all the PBPK modeling, and also cross-validate the MRI study, the non-invasive MRI study, for drug transit and motility.

With that, I stop and take of course questions. Thank you very much.

DR. LIONBERGER: Thank you, Duxin. Questions? Cindy?

DR. BUHSE: Yes. When you talk about doing your GI studies with the modified-release products, different manufacturers often have different release mechanisms for their modified-release products. Do you envision having to actually repeat these complicated clinical trials for all

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the different release mechanisms? Or do you think you can do some, and then do some in vitro work to try to compare that?

DR. SUN: Yes. So that's a good question. The idea will be that's not feasible to do the study as a routine BE standard. That's just way too slow, way too expensive. The idea is, let's gather the different class of compound and data to have confidence. Then eventually the gold standard has to be blood concentration.

Then how do we use blood concentration compare to mimic clearly? Ideally, then, we have datasets to validate all the PBPK model or in vitro test model. So ideally, we have different datasets, IR, MR, local acting. So that's the minimum I say we should have. We don't have any for last 50 years.

If we want more than that, then perhaps then different BCS class compound, we need to have each class compound have a representative, but that's another few compound. So that's the ideal solution. But I think if we don't have that much

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effort need to go forward, but minimally we should have an MR drug product to get that down, put in the public, let everybody use that data to validate their condition, in vitro condition and model.

DR. LIONBERGER: So when you say absorption composite appearance rate, do you need some kind of oral solution to deconvolute that, or is this something you could obtain from just analysis of plasma data?

DR. SUN: Ideally, so ideally you have another arm for oral solution, though, because then basically you have a brand, generic, and also oral solution. Then you have an additional arm. In that way, you can against the oral solution to do deconvolution, that have a few advantages. Number one is really to reduce the variability because you see each individual subject to get rid of our variability. Number two is really to deconvolute much more accurately.

Of course, you can also use the literature data with IV data or other IR release formulation to do the deconvolution. But that's perhaps

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against the average rather than individual. So you have an advantage and disadvantage.

DR. CONNER: When you use your oral solution as your baseline for deconvolution, do you pay attention to how you do the oral solution? Because we have a tradition of assuming that an oral solution is uncomplicated. There's no possibility you can have any change in bioavailability.

But then, quite a few years ago, we came along with discoveries on things like sorbitol, where certain drug substances in an oral solution can be -- their bioavailability can be affected by excipients, especially -- the alcohol sugars are the ones we are most familiar with. So don't you have to take that into account?

You can't just kind of blindly go into that type of drug and say, oh, any oral solution is fine, whereas two investigators using different extemporaneously compounded oral solutions could come up with very different results.

DR. SUN: True. I think in FDA, the old days said the oral solution is self-evident.

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Right? Perhaps that's not true. A lot of time we have a precipitation.

So the proposal I have is two things. One is when we do the intubation, we should also do oral solution intubation. We know exactly what's going on. That's actually very valid. Too bad the data we have, currently have, we're going to publish, we have a solution arm, but we did not do the intubation. We thought we don't need it.

So right now, we will look back the data. We really need an intubation for dosage form and a solution. Then we get a good idea. The solution, oral solution, will give you deconvolution because that will mimic all the transit and everything, metabolism. I think is actually better, even better, than IV. You're right.

DR. LIONBERGER: Thank you. So our next speaker is Chetan Pujara from Allergan.

Presentation – Chetan Pujara

DR. PUJARA: First of all, thank you to the FDA and Dr. Lionberger for inviting me to present here. I really appreciate that. And my talk's

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going to be on nonbiological complex drugs. And I want to further highlight -- I think there's been enough presentations on complex drugs, but I want to further highlight the challenges in the assessment of similarity or equivalence of ophthalmic emulsions.

A real quick declaration of interest from the NBCD working group. I'm not going to read through this. It will be part of the slides that will be posted. So I'll move on.

So the outline of my talk, I'll quickly introduce what nonbiological complex drugs mean. And then we'll talk about emulsions as complex dosage forms. And I feel strange standing in front of Ken Morris and Steve Byrn and others talking about emulsions. They're the ones who taught me all this. And I'll spend a little bit of time on assessment of similarity and equivalence of ophthalmic emulsions.

So I think there's good recognition that we have small molecule drugs, tablets, capsules, et cetera, that are formulated, and we have

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biologicals that are considered complex drugs. More recently the term -- or yes, I guess the term nonbiological complex drugs is starting to gain popularity. There was an article also published on this.

At a very high level, NBCDs constitute of a multitude of closely related structures. The entire complex is the active pharmaceutical ingredient. I think Dr. Amidon mentioned earlier it's not just a drug, it's the drug product.

The properties cannot be fully characterized by physical-chemical analysis. And it was good to see Dr. Lionberger talk about Q3, talk about microstructure analysis. The well-controlled, robust manufacturing process is also fundamental to reproduce the innovator's product. And that's something I want to further emphasize as we go through the few slides that I have.

So with respect to assessment of similarity or equivalence for nonbiological complex drugs, we believe that new knowledge and policies need to be created. I think practically everyone in this room

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probably knows what an emulsion is, but I'll still go through what they are, and then talk a little bit about how we can affect them.

An emulsion is a multi-phase system. I think we all know that it contains an oil phase, an aqueous phase, an interface consisting of surfactants and other stabilizing polymers, micellar structures.

So there's a good cartoon here, and what I want to show on this cartoon is you have oil globules, as I just stated. And in this case, I've just used castor oil as the oil. And the drug is usually dissolved in the oil. You have an aqueous phase.

Obviously, the surfactant is around the corner here. You have polymers stabilizing the entire system. You have water-soluble additives for various reasons. And of course there's drug partitioned into the aqueous phase as well.

So the drug, of course, can then be distributed in all these phases, whether it be in the oil or in the aqueous phase, or within the

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surfactant and micellar structures. And we've seen that for some of the molecules that I worked with.

Now, the amount of drug in each of these phases is an equilibrium, and a dynamic equilibrium, and can shift based on external environment. And I think that's quite common knowledge, that heat and shear and chemical interactions can affect that.

What's also important to mention here is the manufacturing process is very critical to establish the oil droplet size. And I think every time we make a vinaigrette, I think we know that you need to use a certain manufacturing process.

The surfactant and oil interactions are affected by the way emulsions are made. The polymer oil and surfactant interactions are affected, depending on how the material is made. And then the drug distribution nature of the phases.

That's an emulsion. Now with respect to ophthalmic emulsions -- and I'm not going to go through this slide, well, except to say that I

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think it's well-recognized in academia, FDA, and industry that ophthalmic emulsions are complex dosage forms. I have some references here, and I threw in Dr. Lionberger's reference as well.

To further talk about ophthalmic emulsions, they are complex systems, as we just discussed by an emulsion itself. But with respect to ophthalmic emulsions, they are used to deliver poorly soluble drugs to the eye, a complex organ with multiple target tissues.

These emulsions are locally-acting with negligible systemic levels, so PK bioequivalence is generally not possible. The residence time is short, with complex absorption pathways. So a traditional in vitro dissolution test may not be good enough. In fact, I think I can probably say it will not be good enough for in vivo performance prediction purposes.

Then as we just discussed, manufacturing processes can affect emulsion characteristics. But I would submit to you that it would also affect safety, emulsion safety and tolerability, and

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performance by altering drug distribution kinetics in the emulsion. So that's an important aspect to remember about ophthalmic emulsions.

So I'll spend a couple of minutes on this slide. There have been recent FDA draft guidances in ophthalmic emulsions, as Dr. Lionberger presented earlier at 9:00 today, and they seem to be acknowledging the complexity of ophthalmic emulsions.

The complexity is coming from a standpoint of physical-chemical characterization to show equivalence. And as I mentioned earlier, we have Q1 and Q2, and seeing Q3, which is understanding the microstructure of emulsions, is critical.

I'll submit to you that complex -- depending on the type of dosage form, the complexity is obviously going to be different. So it's going to be both the dosage form and the intended use of the dosage form, and of course, the intended performance of the dosage form.

So with respect to that, I would say that ophthalmic emulsions are complex, and so a clear

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link in these guidances to in vivo performance is still missing. And it's also deficient in details on how robust these characterization methods need to be.

What I mean by that is several years ago, I think, when I was part of PQRI, we published particle size methodology and we indicated how different particle size methods can give you different results. And this was just for solid particles.

If you take an emulsion, as I showed the little cartoon there, it's malleable, and the characterization methods can affect how these emulsions will perform in the method. So both the sampling characteristics and the way the emulsion is measured, or determine the particle size, will be affected by the instrument, but also the parameters that are used much more than, I would say, a solid particle.

So what that leads me to say is, and we have obviously done some research on this, that we can take disparate emulsions and show that they are

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similar just by changing the parameters with which one can determine the particle size. So the robustness of these characterization methods is very important.

Further understanding of locally-acting ophthalmic emulsions is necessary to create scientifically robust guidance with respect to assessment of similarity or equivalence of ophthalmic emulsions. We believe that. So I would submit to the panel here that research in the following areas would be a good first step.

In vitro drug release methods that can be linked to in vivo performance -- I think we've already heard a couple of talks on this earlier today, and probably more to come. I saw Diane's topic. She's going to talk about in vitro-in vivo methods and how we can link them.

With respect to ophthalmic dosage forms, it's even more critical because it's locally acting. There are no methods, as far as I know, that are available. And most of the methods basically take a 900 mL dissolution bath and they

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try to miniaturize it, and I don't think that's probably sufficient.

So this is an area that's ripe for research. And I'm looking at all the great professors sitting in the front here, and I would submit that a lot can be learned here to make better drug products available to patients.

Then, as I mentioned earlier, robust emulsion characterization methods, research in this area would also be a good first step -- for example, drug distribution. And in the recent update to the guidance, I noticed that that's there in terms of how the microstructures can affect. Droplet size I already talked about. And of course, the intention of developing better methods is to provide meaningful information on impact of in vivo performance.

So with that, I have four seconds remaining. I will stop and thank the panel, and take any questions.

DR. LIONBERGER: Thank you. So in terms of the in vitro release method, what do you think are

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some characteristics of a good in vitro release method for an ophthalmic product? And to your knowledge, do any of the approved brand products have good in vitro release methods?

DR. PUJARA: Yes. That's a very good question. I'm not aware of any good in vitro methods in the ophthalmic area. You're absolutely right. Typically, companies would use in vivo methods to further understand because we can get an assessment of both tolerability of the dosage form, because this is a locally-acting drug, and we can understand in which tissues these drugs are going into.

We've not spent much time in developing in vitro methods because this is an area that I think is -- I think we need some disruptive technologies to further advance the science in this area, and we haven't invested a whole lot in it. However, as I mentioned, for development purposes, we typically do use in vivo methods.

DR. LIONBERGER: Thank you very much.

DR. PUJARA: Great. Thank you very much.

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DR. LIONBERGER: So our next speaker is Professor Catherine Sherwin from the University of Utah.

Presentation – Catherine Sherwin

DR. SHERWIN: Good morning, everyone. And a slight change of topic and a slight change of direction for my talk, but hopefully very of interest to everyone, and also very relevant to me in my research group. I want to talk about issues associated with children and generic drugs. I have nothing to disclose.

Some things that we're concerned about, those of us who work in pediatrics and pediatric clinical pharmacology, is what are the differences between the generic drugs and the brands. And I'm a big fan of generics. I'm an advocate for them. I think they are needed, vitally needed. But in some circumstances in pediatrics this is becoming very difficult with regards to the clinical perspective, the parents' perspective, and then also the perspective of the child.

So is it always good that these are cheaper

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and always available? Are they just as good? And we've heard lots of very in-depth scientific presentations yesterday and also this morning about oral absorption. And in that circumstance, are we considering differences in maturation within children and their different maturation of the gastrointestinal system?

So can we maintain the quality and reduce healthcare costs if we use more generics? And I think we can. I just think we need more consideration, particularly on the pediatric side.

So what criteria should we have for switching from brand to generic drugs, particularly in a pediatric population? And do we have a therapeutic switch? And if we do these, how do they differ and is this relevant for that patient population?

So the generic approval differences are available within the brand drug. For pediatric indications, they usually test in adults first, and this is obviously due to ethical considerations and constraints. We can't get a child, line up a whole

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bunch of children, and tell them to volunteer to take a drug that they don't need and they won't need. I can't see many parents consenting to see that happen.

Also very difficult to take the number of blood samples that we need to look at the PK within that patient population. So we are definitely relying on the information that comes from adults.

Bioequivalence is based on kinetics and the pharmaceutics. We've heard about dissolution. We've heard about absorption. These things vary in children. They vary in the neonatal population. They vary between ages of children and between a child that's a 2-year-old versus a 10-year-old. So does this mean that we need to look at differences in repeating assessments for steady states of drugs within children? And how do we compare the therapeutic effectiveness between drug A and drug B within this patient population?

So we do a lot of bioequivalence evaluation study design. We have very set, very specific criteria to achieve that. It's done very

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standardized within the Office of Generic Drugs. There's a lot of opportunities, and Dr. Lionberger outlined this morning all the initiatives that are being done. They do careful controlled crossover studies. We do comparisons between the brands of the generics.

The patients typically are young, healthy adult and mainly male, and definitely not in the pediatric realm. We're looking at comparisons between AUC, Cmax. We look at measurement, and we look at the half-lives between those patient populations.

We know within pediatrics those half-lives for many of these drugs actually vary. And depending on the age of the child, we have a variability in clearance. We have a variability in absorption.

So it becomes very difficult when you're trying to equivalate these from an adult population across into pediatrics. We typically, in the adult population doing crossover designs, look at different half-lives. And all of those becomes

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fundamentally different within the pediatric side.
Substitution is not all the same. And something that clinicians I work with talk about a lot is the difference between generic substitution and therapeutic substitution. And substitution with generic substitution is substitution of a drug without market exclusivity, but the drug has the same active ingredient as the branded product.
Within therapeutic substitution, it substitutes a drug considered therapeutic equivalent to one that has been ordered. And the basis is, similarity is not always clear or focused with regards to pediatric patients, and I'll give you examples shortly on that.
So why would a clinician want to fight this, or why would they might not think that this is something that actually wants to be done? A branded formulation is pediatric-friendly so you usually are trying to have a solution or a suspension, something chewable.
What we find sometimes in the patient population, and I see this in my own children, you

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have a brand that you're prescribed. All of a sudden you get the generic version. It goes from being an oral square tablet to a round tablet. My son freaks out because he's used to the square one. He doesn't want the oval one.
You have differences in taste. One minute the formulation tastes like strawberry. The next minute it tastes like cherry. And in a pediatric population, that's highly concerning. If we're talking here about the equivalence, all of the kinetics, that's fine when we're looking at adults and we're saying okay, the kinetics are the same. But when we break it down to the formulation differences that we see within the pediatric, that becomes a difficulty when we switch between a brand and a generic.
So there's few pediatric therapeutic studies that have looked at the branded drug to support different age groups in the patients. And this isn't always considered when we're doing these studies and when we're trying to equivalate, and when we're looking at differences in absorption,

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and if a drug has a narrow therapeutic index, how that's actually going to equivalate within a pediatric population.
Some examples. A 3-month-old child who has probable GERD, the doctor orders Prevacid and omeprazole is dispensed. Are these therapeutically equivalent? Have they been studied? Do we know this? Omeprazole's suspension has never been labeled for children less than 1 year old.
For a lot of infants, newborn infants, GERD is a very serious consideration that the doctors want to treat. PPIs are quite commonly given. But we know they have variable kinetics in all ages. And we know that the formulations are different. And we know that these have not been tested in children this young.
Other differences, and something else that is irrelevant, particularly in the pediatric side, is differences in the pharmacogenomics. We know that the PPIs are mostly cleared by CYP2C19 and not as much by 3A4. And all know that there are ontogeny or maturational differences in the

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pediatric populations between a 3-year-old with regards to their CPY2C19 level versus a 5-year-old. And that's something that becomes an issue if you switch between these drugs when we haven't got this information available.
So is therapeutic switching appropriate? What are the data? Should they be interchangeable? In these children who are 3 months old, is this the same? Is this therapeutically equivalent? So these are the questions that I'm asking and that I want to help answer.
So therapeutic switches requires a knowledge of the pharmacology. It requires clinical trials. And as Dr. Lionberger said this morning, this is difficult to do some of these studies, particularly in the population, but we do have access to databases, insurance claims information, electronic medical records. The information is there; we just need to actually find a way to access it.
Some of the areas that we have of concern are the psychoactive drugs. Cardiac drugs are being more and more used in younger populations as

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the obesity epidemic grows and these children are developing cardiac conditions. We're using cardiac drugs that have never been tested in children.

Antidepressants, the same, being used in younger, younger children where we've never done these clinical trials or done these clinical studies. Other areas of concern -- transplants and oncology and a lot of drugs that we're using in those that we're extrapolating the data from adults and using them down in pediatric patients.

Generics have a role. As I say, I am a fan of generics in pediatric medicine. They are desperately needed, particularly within the underserved populations, and for these children to have access to this medication. But we need to have consideration for this.

We need to look at the reduction in medical costs as being a benefit, and again, that was covered earlier this morning. But we also need to look at any unanticipated health costs which can come when we use these drugs in a pediatric population where we have no clinical information,

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where we don't have this information to know the differences.

There's few studies done in pediatrics where we compare drug A and drug B, much less looking at cost-effectiveness. And is it cost-effectiveness in some of these cases to change a child from a brand drug to a generic if we know that they may have an increased likelihood of an adverse event?

Without pediatric studies about the pediatric label, we have the exclusivity which the FDA brought in through the BPCA and the FDAMA a few years ago, which has made a big change to industry having to do some of these pediatric studies.

But we still don't have as much information as we need within this population. So generic switches are seldom based on pediatric data. It's usually the data that's been gathered from adult studies.

So in my summary, I am an advocate of doing, obviously, pediatric research. I would like us to be able to use the data that we currently have available. Again, as Dr. Lionberger said this

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morning, we have data in these electronic medical records. We have data in these insurance claim bases. We have modeling and simulation which we can use. We can extrapolate the data. We can do models. We can take the data from the adult side and extrapolate it down to children.

But I'd like us to look more at the differences between the innovative and generic drugs and how this affects substitutions within this patient population. How do we distinguish between a therapeutic and a generic substitution when treating children?

How do clinicians make that decision? How do the pharmacists who are filling the scrips make those decisions? How can we identify the general factors to consider for a therapeutic switch and a generic switch?

I think there's a lot of innovations that the FDA, through their granting mechanisms, are actually starting to try and look at these things. And I think this is something that we really need to be doing, and not only in pediatric population,

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but also within pregnant women, breastfeeding women, and geriatrics as well.

My last point is to select therapeutic areas for generic substitution increase of adverse events and to look at those more closely so that we can prevent those worse outcomes from occurring. And that would be me.

DR. LIONBERGER: Thank you. Questions?

DR. STODART: Thank you for your presentation. In general, do you see any particular age range or ethnicity that is more vulnerable than others?

DR. SHERWIN: So the age range that, from my perspective that is the most vulnerable is the neonatal age range and the under the age of 2. And ethnicity, I live in Utah and I work in Utah, which is a very homogenous population.

But definitely within the studies that we do, we see issues in the Pacific island population and also in the Native American Indian population within our region. And that's most of my experience in America.

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DR. LIONBERGER: When we talk about differences between the brand and generic, as Gordon has mentioned, it's really a product formulation that's different. And I think a lot of the -- some of the discussion things like clearance. Right?

You don't think that the clearance of the active ingredient is going to be any different in whichever patient the product is given. So can you identify the specific product differences that you think are of concern for substitution in different populations?

DR. SHERWIN: So the one that we've done the most research on, and one actually which we have a grant through your office right now, is looking at the immunosuppressants and looking at tacrolimus. And we have identified some differences in the very younger age group patients, around 2-year-olds.

Above that, it does tend to equivalate to adults. But it's definitely in that 2- to 3-year-old range that we do see differences, which is obviously related back to maturation within that

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patient population.

DR. CONNER: Could you give a little bit more detail on the differences? And I won't go to therapeutic substitution, which is not a generic drugs issue, because that's a substitution that's made by the physician by writing a new order, a new prescription.

So it has all of the medical monitoring that any other prescription would have but the generic substitution, which does not necessarily involve the physician, but is done at the pharmacy or institutional level.

Also I'd like your ideas on if, you know for the generic substitution or generic products, if you feel that there isn't enough information in pediatrics, what would your suggestions be about going and getting it? Knowing that the generic product, when it comes in as a new application, has probably never been --

DR. SHERWIN: Never been used.

DR. CONNER: -- published or seen or is the world literature. It's a brand-new formulation

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that is attempting to copy, in a way, the existing product that's hopefully very successful in patients in the marketplace.

DR. SHERWIN: So something that we see within our institution is, particularly for one of the studies that we're doing right now, looking at Botox for children with muscular spasticity.

We've seen, actually, a difference in adverse events within the difference between the brand and the generic. So there's something that we're seeing within a pediatric population that hasn't actually been seen much in adults.

We've been looking at other specifics and other drugs that we see differences in. Some of the antibiotics that we see used within our younger patient population is different to what we see in our older patients. So within our neonatal population, things like vancomycin, we see a difference within the kinetics, depending on whether the doctors are ordering the brand versus the generic. And we have had reports from our doctors.

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The way that we have been addressing this is actually pulling data from our large electronic data warehouse. And we pull information on whether the patient had the brand, whether they had the generic.

We look at the outcomes. We look at when did they switch? Why did they switch? What were the differences? What were the indications? Was there a therapeutic reason to switch? Was there a concern from the patient about which drug they were on?

It's hard for us. We don't actually work on the outpatient side, where I think there's actually probably a lot more of these concerns within the patient population from parents. And we do get that back through our patient pharmacy therapeutics committee, but we don't see it much. I see more the inpatient side.

DR. CONNER: It seems to me some of the examples you just cited were injectables.

DR. SHERWIN: Um-hmm.

DR. CONNER: The vancomycin, I assume you

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mean the injectable use of vancomycin.
DR. SHERWIN: Um-hmm.
DR. CONNER: Another one, the Botox, I think is an injectable as well.
DR. SHERWIN: Um-hmm. Injectable, yes. IM.
DR. CONNER: So a generic of that would be virtually identical as far as its inactive ingredients.
DR. SHERWIN: Um-hmm.
DR. CONNER: The active ingredients -- I think the Botox is a somewhat complex drug substance.
DR. SHERWIN: Yes.
DR. CONNER: So your problem, if it exists, could be there. But as far as generics go, they're essentially a very simple approach of trying to copy, literally copy --
DR. SHERWIN: Copy.
DR. CONNER: -- an injectable point by point.
DR. SHERWIN: Yes.
DR. CONNER: Unlike some oral products, where you have different excipients.

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DR. SHERWIN: You have absorption and everything else. Yes. And that's something that we're looking at, is with regards to excipients within the neonatal population in particular, that is of concern, is the excipients that are used within the formulations. I don't do that much in oral drugs because I am working in neonatal populations, so we typically are using more IV and IM.
But there are ones where we still have concerns, mainly from the clinicians who say, I don't want to give my patient this brand of tacrolimus because I want to use the generic. Or you have the opposite. I have one doctor who will only use the generic, will not use the brand. So we get differences in perception which I think come from the clinicians in their obviously own experience.
DR. PINHEIRO: Just a quick follow-up on what you mentioned earlier. Did you say that in the databases that you've been considering, you have information on the

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indication -- sorry -- reason for switching?
DR. SHERWIN: Yes. A lot of the doctors have to write -- if they change from one specific drug brand to another, and especially if there's a cost association, they actually have to justify why they make that change.
DR. PINHEIRO: Great. Thank you.
DR. LIONBERGER: All right. Thank you very much.
Sorry. Ruth?
DR. BARRATT: I have one question, Rob. So these are a lot of suggestions, and quite varied type of studies that you're suggesting.
DR. SHERWIN: Of course.
DR. BARRATT: So trying to wrap my brain around this to -- do you have any sense of, if not priorities or areas where you can make the most impact, maybe top two? Because it could be surveys, it could be EHR.
DR. SHERWIN: Yes.
DR. BARRATT: It could be assays. It could be palatability studies.

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DR. SHERWIN: Yes. So my priority would be particularly with the medicines where there are high costs to the family and looking to provide, I guess, confidence within the fact that the generic is going to work within the pediatric population.
We have a lot of very expensive brand drugs that are used. Kalydeco is one used for CF that is tremendously expensive. Lupron is another one that I'm actually already doing with the FDA which is tremendously expensive.
So any information that we can gain for, one, either working towards having a generic available or, two, providing confidence, if there is a generic available, for the clinicians to use those within a pediatric population.
The argument I get back is, well, it's never been tested in children. It's a generic. Why would I use it in my patients? So I think we need to provide that confidence and that evidence to the clinicians.
DR. LIONBERGER: All right. Thank you very much.

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(Applause.)
DR. LIONBERGER: So our next speaker is Dr. Ajaz Hussain, who is representing NIPTE. Presentation –
Ajaz Hussain
DR. HUSSAIN: Good morning. The discussions earlier today, I think, highlighted some very important aspects. So I wanted to start with summarizing some of my takeaway from listening to those discussions.
Drug shortages expected to continue was one of the messages Dr. Fischer said, and that we need a plan to deal with that in a more efficient basis. I'm a pharmacist by training, and I think NIPTE focuses on pharmaceutical technology and education from a pharmaceutical technology perspective. A clinical community thinking about planning to deal with drug shortages on an ongoing basis is not an acceptable situation.
I think confidence in substitution has been a work in progress, and Rob Lionberger's talk really highlighted some of the significant advances Office of Generic Drugs has made in this area. And

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I think it is work in progress, and we need to do more in that area.
I think the point that -- Dale Conner asked that question; I want to hone in on that question to frame the talks that NIPTE wish to share with you -- is clinical relevance of QC methods. We cannot ignore that question. It is part and parcel of everything we do. And every method we may develop for bioequivalence, there is a built-in assumption that the product you're using is the right product for that method.
What we have learned, especially -- Gordon is not here, but Gordon, before Dr. Amidon's sabbatical, I was with him at FDA then. The advantage we had was, we had the biopharm filing room right next to my office. We were able to review every NDA application that was submitted for the BCS guidance finalization.
What we found was that dissolution is product-specific, formulation-specific. Seventy percent of the time it's over-discriminating, but 30 percent of the time it's not. And the

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experiments that we did next were sorbitol and excipients came out of that sort of analysis. So that knowledge base is not really available often for us.
I think keeping that in mind, what I would like to do is really build in the point that drug shortages are often due to manufacturing difficulty. I think when I was at FDA 2002, looking at those reasons for shortages are the same.
Manufacturing difficult is the foundation. And manufacturing assessment is based on QC methods. So you cannot ignore QC methods. You cannot ignore formulation even when you're developing bioequivalence methodologies for assessing these things. So that's the heart of the issue here.
So again, good morning. My name is Ajaz Hussain. And I represent NIPTE as their president. I work, just for disclosure, devote 50 percent of my time to NIPTE and 50 percent of my time is a consulting practice which is completely focused at

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the moment on complex generics and biosimilars. And following my FDA tenure, I had an opportunity to work for Sandoz Biopharmaceuticals, leading their biocomplex generics and biosimilar program.
In my practice for the last 10 years, I just wanted to share with you one definition of complexity. I think we think about complex dosage forms. I think that's a good way of looking at it. But complexity depends on available knowledge and available expertise.
So if I think about something which is complex, something which is complicated, something which is simple, something which is complicated, good practices work for that. Something which is simple, best practices work for that. Something which is complex, you have emerging practices. Good practices don't work for complex systems. So the development and assessment has to reduce the complexity to be complicated so that good practices work.
With that in mind, let me quickly share with you some thoughts. Quickly, NIPTE is a 501(c)(3)

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non-profit organization. There are 15 schools, and the 16th school will be joining, and Ken Morris represents the new school that is joining up. So we bring together pharmacy and engineering and medical schools especially to focus on improving quality, lowering cost.

It is completely funded by FDA through a U01 grant so far, so I think we want to acknowledge FDA funding. And we made it a point to come to this discussion without focusing that NIPTE should be funded for these products. So we wanted to have a general discussion for this.

The point I think is important to remember is, US FDA strategy response to maximizing how generics meet public health needs is really fairly well-articulated. I think that Rob Lionberger's presentation on how he's progressing is very impressive. And I think looking at the points Dr. Woodcock made at the recent congressional testimony on the 4th of February, first, generics is a public health priority. And I think that's an important element.

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GDUFA 2 negotiations, thinking of pre-ANDA process; clearly pre-ANDA process will not likely to be available for every applicant because sheer volume of that. Pre-ANDA is an opportunity in one sense, like end of phase 2 meeting on the new drug side. So think about that. I think Ken Morris will cover on that.

I think today we are here for looking at prioritization of research at this meeting, but I also wanted to emphasize the need for additional regulatory -- regulation is the words Dr. Woodcock used, but I say better assurance of quality in an increasingly globalized industry. One voice of quality is another major opportunity, and all these pieces really need to come together.

So in the challenges, you have organized this conference very well. I'm not going to go through this slide, but I think the NIPTE presentations you have are covering multiple aspects of the topics that you have outlined.

The key aspect I think I want to emphasize is public perceptions are shaped by the few errors

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and recalls. Even if we do 95, 97 percent of our job fantastic, nobody is going to give us credit for that. They will count the mistakes we make. Unfortunately, that's what we have to deal with, and I think we are up to that challenge.

I think stark reminder of the perception impact, I think, is the color and shape guidance that FDA had to finalize, and the impact it has on patient perceptions.

Totality of evidence is increasingly the dominant part for complex generics. Complexity is increasing generally. And I'll urge you to think about complexity as emerging practices. You have to reduce complexity to be complicated for good practices to work. And therapeutic equivalence increasingly demands notable attention to integration of product and process, design with orthogonal analytics in vitro, and when necessary, in vivo.

Without that integration, the risk of making incorrect decisions is high. Knowledge base and decision-making process pertaining to integration

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of evidence really is the topic we wish to share with you as important considerations as you think about your program going forward.

Some examples, simply some examples I wanted to share with you. I think if I look at the guidance on methylphenidate hydrochloride, we had a setback. We came with the modified guidance. And then we have involved or incorporated subject by formulation interaction as a requirement in terms of the bioequivalence.

Is that the right question to ask? I don't have an answer for that, but having spent a lot of time thinking about subject drug formulation interaction during my FDA days, isn't formulation science a better answer, would be a question I would like you to consider. I think if I look at mesalamine, the draft guidance is asking for the applicant to provide high variability and bioequivalence parameters.

I'm going back and looking at the work of Cindy's lab in St. Louis, when I was there, we did. I think the mechanism for the variability can be

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identified. Isn't there a better way of dealing with that and integrating the formulation science aspects to this?

I think I had an opportunity to guide a client through the first approval of the nasal spray product that I'm talking about. I think this is the right question, the right time, can be significant benefit here.

So I think need for integration and clarity is important from these aspects. And I will skip through a number of things to go back to the summary slide, maybe, to think about the totality of efforts that need to go in.

I think the regulatory science agenda, really, if you -- I request you to consider locating a portion of your funding and prioritization to knowledge base and standards for integration development across the product class categories that you have.

I really would leave it at that to say that to achieve the public health objective of first generics right on time, right question at the right

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time is necessary. One voice of quality. And we believe the missing element here is the integration and knowledge management that needs your consideration. Thank you

DR. LIONBERGER: Thank you very much.

So can you clarify a little bit about what types of knowledge you'd see in this?

DR. HUSSAIN: Sure. I think immediate high priority in terms of that would be what we have been looking at. Just based on your research, I think you're looking at Q1, Q2, Q3 aspects. And actually moving away from Q3 aspects for inhalation and so forth are important.

So the knowledge base that is missing there is the excipients. Our excipients are controlled based on certificate of analysis that actually do not tell you anything about the functionality. Therefore, in knowledge base of excipients and how to use those excipients in those settings would be important.

I think excipient knowledge base is important all across, but one can prioritize to the

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high areas and then think about that. We tend to focus on excipients only in terms of oral, but excipients get more and more important for topical, inhalation dosage form and so forth. That would be one area.

The other area, really, I think, from knowledge management is, I think, what are the right questions to be asked at the right time? I think, given that we are using more analytics, especially, I think, if I look at my thought process in helping Sandoz go through first in/last out. We have to use orthogonal analytics to characterize the RLD and show similarity. Those analytics are above and beyond those of compendial and other trace requirements. That opens companies and FDA vulnerable to challenge, continued challenge.

So what is the right knowledge base of -- what knowledge base guides us through what are the right analytics and how do we address that, is another example. But I think integrating the pieces together is something we struggle. We often

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tend to be focused on one particular area. Cutting across and connecting the dots across multiple disciplines is a challenge, and I think we can do some significant focused efforts there.

DR. BOAM: Do you have any thoughts about how to make this knowledge base visible to everybody in the sense that for standards we have our guidances, or we have it at the USP or ASTM?

Obviously, for knowledge we've often relied on publications, the literature, I would say. But how would you envision making knowledge a little bit more transparent, maybe? Or what's important the literature and what isn't, or et cetera?

DR. HUSSAIN: I think literature clearly is part of the knowledge base, but it's not sufficiently specific to help guide informed development and other decisions. Draft guidances -- guidances are knowledge summaries. And if I simply make an -- to take an example, that every dissolution method you recommend in your draft guidance is formulation-specific, is derived from that of the RLD or what's in the USP, the

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generic industry has no choice but to use that as a target. Then they stop thinking about, is that method specific to this formulation? Or my formulation would be dealt with that.

So if we can think about your draft guidances, if you can think about a summary scientific assessment, scientific knowledge base that could be a white paper that gets associated with that, it could be specifically targeted for each of those guidances. What are the other scientific considerations?

Or it could be, I think, as Ken Morris will talk about that in more detail, is it could be computerized information system which has the repository of data, but also the rules of what are the questions to be asked, what's the logic, and going in the direction of an expert system also.

So there are different ways of looking at that. And where you start from and where we want to go will depend on, I think, what topic we choose to work on that.

DR. LIONBERGER: Thanks very much, Ajaz.

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So our next speaker is Professor Stephen Byrn from Purdue University, also representing NIPTE.

Presentation – Stephen Byrn

DR. BYRN: Thank you very much. I'm going to try to embellish on some of the questions that were just asked, really, one about knowledge management and one about specific areas of investigation. I'm also going to try to hit a high point on the pediatric formulations.

So the overall title of this part of the NIPTE presentation is, "A Mechanism for an Integrated Approach of Formulation Research, Knowledge Management and Knowledge Sharing, being proposed and advanced by NIPTE."

We don't probably need to spend tons of time on this slide. This slide is just highlighting a complexity of formulation science. On the one hand, we have performance issues, reliability, formulation stability, bioavailability, safety, and then on the other hand, we have processes.

The design of the formulation, I think, is a

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critical element. Characterization, we talked about analytical recently. Prior knowledge in the literature and in scientific meetings. And then all of the approval and compliance decisions that come into play. So all these combined, obviously, as we've been talking about, make it a very complex area.

The issues are broad, and the ones I'm going to try to talk about relate to fundamental understanding, and specifically the bullets, the ones with the lines. The structure, obviously I'm going to try to hit solid state chemistry, reactions that can occur, as well as the components like the excipients. And then the design, the entire design of the formulation, structure, performance, behavior, all of those issues.

Listed with the bullet points are four areas of a special concern, the idea that acid-base reactions can occur, especially with drugs and excipients; the whole nanoparticle field; emulsion formulations that Dr. Pujara already covered; and control of these complex formulations.

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Just some additional issues. Pediatrics, stability, failure modes are often not fully explored. We've been doing quite a bit of failure mode work in the abuse-deterrent area, but still generally they're not fully explored. And then Dr. Morris is going to cover the question-based review and the right questions at the right time.

So this slide is a summary of what I'm going to present in the next few slides. It highlights complex or problem formulations that we know about. It's a lesson that can lead us to more understanding as we go into the future. We don't want to forget about history, is what I'm saying.

So on the controlled release side, we've got both the bupropion, Wellbutrin, which we've already heard a little bit about, and the methylphenidate area.

On the emulsion-base formulations that have already been covered, we had the pretty well-known Neoral situation. We have the nanoparticle side. And then there's tremendous interest in BCS Class II, using the old system of formulations of

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those products, because those, especially in the antiviral area, those are tremendously important products. And of course, we're curing some antiviral diseases now with BCS Class II products. And then I already mentioned failure mode.

So I'm going to go into some specific historical examples. Some of these have been addressed earlier, and these are quite interesting. This is the Neoral case. And you can see the first vial on the left is Neoral in water. And a second vial is another product in water. And you can see the particle size is tremendously different in those two vials.

This reminds me of a quote from Yogi Berra where he said, "I can observe a lot by just watching."

(Laughter.)

DR. BYRN: Okay. So we can see a lot about the particle size by just watching these two. And if we got to apple juice, you see the same, a big difference. And then more similarity in the last two vials.

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Clearly, there's a structural particle size variation of the type that Dr. Pujara was talking about. We need to understand that better. We need to understand how those formulations are performing and what role the particle size. And Dr. Morris will talk about QbR related to that.

This is a famous bupropion/ Wellbutrin case. In that case, one thought is that it's structurally related to the two different formulations. The XL 300 bupropion dose-dumped, whereas the Wellbutrin formulation, which was made by different technology and had a different structure, the membrane technology did not dose-dump.

Again, QbR questions in that area and just specifically trying to figure out what the structure of those two formulations are, the manufacturing, and how those parameters lead to different behavior.

Here is one on the pediatric side. This we found in a magazine in one of our children, when we took one of children to the doctor. We found this ad in a magazine. And here we have a young lady.

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I guess she's about 10 or 12. And the ad is quite interesting.

These are two products now. They're bioequivalent, Metadate and Concerta. And what they're advancing on this ad is that the Metadate is better blood levels in the critical learning areas. So it's again -- and these two are structurally different formulations. The Metadate is beads, coated beads, and the Concerta is an oral formulation.

Of course, there's tremendous -- there has been historically quite a bit of internet traffic on which of these formulations work best in adult ADHD patients. And perhaps it's related to these levels.

This is not a scientific study, it's an advertising study, but it's pretty interesting to see what people are advancing as different blood levels from different structures of formulation. Just a structural difference in the way they work, really.

Here's the famous ritonavir case.

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Ritonavir, a very important anti-HIV drug, the Magic Johnson drug, crystalized in Form II. After a year and a half on the market -- this is about 15 years ago, and had to be -- the original formulation had to be withdrawn, and there was about a year delay. And if we go through, I'm sorry this isn't a very good picture on the right, but it's similar to that Neoral case.

The bottom flask is the magic surfactant that creates -- when you dissolve this formulation, it creates a clear solution, which would be very small particle size. The top two vials, or Erlenmeyer flasks, are dissolution experiments where the product results in an opaque solution, again similar to the Neoral.

The bottom product is purported to be better and gives higher blood levels. And there's a lot of discussion about precipitation in the GI tract and so on. Again, a very complex formulation that's even affecting precipitation in the GI tract.

Finally, just a quick picture. This is a

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picture of Abraxane, a very important drug for breast cancer. Completely cartoon. From what I can tell in the literature, we don't know what the structure of that particle is, but this is an advanced concept of what the structure might be. Again, there will be generic products to Abraxane in the future, and we need to know more about that product.

I'm going to skip this one and go to a conclusion. Here's my summary slide. So I've been trying to address the mechanism for an integrated approach. And down at the bottom bullet are some deliverables that we believe NIPTE can bring to bear, and it was related to some of the questions.

How are we going to develop this scientific information? One would be either targeted white papers or publications, "what if" scenarios, scenario based research, transdisciplinary elaboration to inform question-based review; and then, two key elements -- a training program, and we envision NIPTE to become the curated knowledge base for formulations, probably a web-based system,

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although this is evolving.

So I'll stop right now. And again, thanks very much for inviting me.

DR. LIONBERGER: Thank you.

DR. UHL: Could you expand a bit more about the knowledge base aspect? I know Cindy had a question, too. So what I heard -- because I appreciate you mentioning -- what you just said expands a little bit on what Ajaz just said.

DR. BYRN: Right.

DR. UHL: Because I'm trying to wrap my head around, what would that look like? Who would own it? How would it be available? These are just --

DR. BYRN: Sure.

DR. UHL: How would you get the data to populate in the first place? So if you could just -- any kind of thinking you guys have related to this.

DR. BYRN: Sure. And other people can elaborate on this, and it's an evolving concept. We're academics, so we're open literature production. So we view it would be open. It could

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be on a website, like the pharmaHUB. It would be a combination of white papers, studies.

I can't get out of my head the idea that therapeutically, like the conazoles -- so all that antifungal conazoles, I can't get it out of my head that those formulations might be somewhat similar. So one structure would be based on drugs that hit certain targets. We would classify those all together, and we would have a white paper or something on formulations.

On the emulsion side, we would break from that and go straight to emulsions, I think, like Dr. Pujara proposed. So we would have -- and Dr. Munson is going to talk about analytical strategies. For example, NMR is very powerful for emulsions. So that would be an aspect also. So I could envision white papers in these different areas, but I think this is all evolving.

DR. UHL: Okay. Thank you.

DR. LIONBERGER: In your talk, you have a bunch of somewhat older examples of product issues. What do you think -- how do you think this

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knowledge base would address the -- prevent or address those type of, say, formulation failures that you tried to illustrate?

DR. BYRN: Sure. Especially in the emulsion area, like Dr. Pujara said, we don't know where the drug is, even. Is it in the oil droplet? Is it in the micelle? Between the components and the micelle? As he pointed out, it's equilibrating, potentially. What controls the particle size of that material? All of that is critical I think. So we would address all of those issues.

I think some of these old ones that I showed probably we know more about, but certainly in the emulsion side we don't know much more. And I don't think we know much about the nanoparticles, either.

DR. CONNER: One of your examples, you made the statement that Metadate CD is bioequivalent to Concerta, I believe. That's simply not true.

DR. BYRN: Okay. Okay, great.

DR. CONNER: It's not rated that way. And I was checking the orange book just to make sure that my memory is --

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DR. BYRN: Yes, okay. Pardon me, yes.
DR. CONNER: Yes, they are two separate RLDs, two separate NDAs. No one has every claimed they are bioequivalent or switchable in any way.
DR. BYRN: Okay. Good catch. Good catch.
DR. UHL: Right. But they're two separate RLDs, so they're competitors, and one is advertising its --
DR. BYRN: Well, that's why the ads are out there.
DR. CONNER: Which makes your example make a lot more sense.
DR. BYRN: Yes. Yes.
DR. CONNER: Because there are two NDA brand name products competing again one another. This one's saying, we have a better profile than that other one that you might prescribe. But it's not like a generic issue.
DR. BYRN: Good point.
DR. BUHSE: So I think this actually brings up -- enhances the question that I was going to ask, is that -- and I'd like to ask a little bit

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more about the training programs you suggest because I think in a variety of presentations we've had today, there still seems to be some sort of fundamental misunderstanding about what a generic is versus a therapeutic equivalent. When is something signaled as substitutable?
It sounds like that we would benefit from some training external to the agency space on these issues. Can you talk about whether your training programs would incorporate that type of training, or what else you meant?
DR. BYRN: So we're thinking of three tiers of training. The first tier would be what you're talking about, general generics, the whole generics 101. And then the second tier that we're thinking about is formulation base, general formulation, understanding substitutions, salt switches, things like that.
Then the third tier would delve into some of these more complex issues related to, say, structure; formulations; why they would work this way or that way; how you vary that; what the new

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formulation strategies coming in the future are; how the agency could gain education in that area so when submissions come, people are well aware of how those formulations work, how they're designed, what their structure is, et cetera.
DR. BUHSE: Thanks for that question. So that's the content of the training?
DR. BYRN: Yes.
DR. BUHSE: What's your thinking of the format of the training?
DR. BYRN: Yes, we've been discussing that also. There's a little bit of a discrepancy. We don't want to do it all distance. We may want to have either all live or a combination of live and distance.
DR. BARRATT: A question. So who exactly is the audience for all of this training?
DR. BYRN: So we envision as both the FDA and industry. And I just want to add a comment. It's clear I'm going to be in level 3, not in generics 101. I'm going to be one of the instructors.

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(Laughter.)
DR. UHL: So to expand on that though -- because, Ruth, that's a good question. And your answer was FDA and industry.
DR. BYRN: Yes. Yes.
DR. UHL: Those are two huge buckets.
DR. BYRN: Right. Exactly.
DR. UHL: So do you have more targeted ideas or --
DR. BYRN: Well, we have a hundred profs in NIPTE, so we think we have capacity to handle quite a bit. But our strategy would be to start small and maybe start a few buckets and build up.
DR. LIONBERGER: All right. Thanks. Anyone? I think it's time for lunch. We will reconvene at 1:00 p.m. for the afternoon session.
(Whereupon, at 12:02 p.m., a lunch recess was taken.)

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A F T E R N O O N S E S S I O N
(1:01 p.m.)
DR. LIONBERGER: Welcome back, everyone, to our afternoon session. It's my intention to start on time, end on time. I know it's Friday afternoon, and if you didn't get a chance to go outside, it's a beautiful day outside. I hate to tell you that, but --
So our first speaker for the afternoon session is Professor Ken Morris from Long Island University, also representing NIPTE. So welcome, Ken.
Presentation – Kenneth Morris
DR. MORRIS: Thanks, Rob. Good afternoon, everybody, and thanks very much for the invitation, Rob and NIPTE. So I'm going to continue discussing some of the themes that Ajaz and Steve discussed before break, but drilling down a little bit more. And this is still focusing on the idea that QbR is really an organizing principle that I'll try to put in context of the larger theme that we've been discussing.

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So I'll start with a quote from Janet Woodcock at the same -- I think the same testimony that Ajaz was talking about. And one of the things she mentioned, or highlighted actually, was in ongoing challenges for generics is that there's a need for more research in the space, and that some drugs lack generic competition because there's no convincing bioequivalence test method available.
Similarly, methods for showing chemical sameness for certain complex drugs are not available. And I'll show an example that is an apparently simple compound that turns out to be more complex, but something that I think some of you in the room are familiar with.
So what does it mean to say that QbR could be an organizing principle? I'll start by saying that QbR and QbD are not independent. They're really joined at the hip. And I know that, as Lawrence and Ajaz and Rob were formulating the QbR approach, it was never intended to be separated from QbD. QbD is the framework within which we all have to be developing our formulations and products

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because those are the principles that have to be adhered to, to have a quality product.
The question-based review allows you to populate the network and populate the framework of QbD. And that's its highest and best use, in my opinion. And all of that is captured at best, or I should say should be captured at best, in the development report, which requires that you have -- and this is really the heart of QbR and QbD, as far as I'm concerned -- which requires that you actually have a good, sound scientific rationale so that you can apply the fundamental principles, prior knowledge, and heuristics to justify and explain what it is that you are designing into your dosage form.
The Q8 and Q6 principles are therefore implicit. And I think, actually, after we had prepared all this, there was an announcement specifying a little bit more, or lending a little more specificity to how Q8 and through 9 and 10 are applied.
Then you create the knowledge base. So some

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of the questions earlier this morning had to do with knowledge base, and I'll try to address them relatively quickly. But the development report and development history has to be a living document because you don't want to restrict companies from improving things because of any barrier, real or perceived, in improving their methods.
So this is complementary to what Ajaz was talking about with respect to analytical methods that are a generation or so behind the existing state of the art that restricts you from improving your product, potentially.
Then the idea that you can use new but also prior knowledge to make decisions requires again that you have a complete history, or at least as complete as possible history, of the project itself. This will also help you in capturing the failure modes, and it will facilitate the sharing of the knowledge between FDA in both review and inspection wings, because we've done this.
Some people had asked -- and I can't remember who now; you've all asked a lot of

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questions, good questions, about the training -- but we had done training for PAT when the PAT guidance came out. We had done unit operation training; Chetan Pujara was part of that at the time. And those were very successful groups. And I think the premise should be included, or should persist, but there are other mechanisms by which we can share knowledge as well.

Let me give you the example I was talking about. So this is from -- there were a couple of advisory committees we had when I was on ACPS on levothyroxine. And this one just highlights the fact that for levothyroxine, there was a very small window. It's a narrow therapeutic index compound by classification, that is, pharmacologic classification. And very small changes in the potency would potentially cause very large changes in the patient outcome.

So Eric Duffy had compiled all the data. And you can see that between manufacturers, as well as within manufacturers, the intra-manufacturing data was showing a broad variety of behavior. And

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the question then arises, well, how do you approach a project like that?

Well, you start with the molecular structure, of course, and then you build on that and look at the structure of whatever the condensed phase is you're working with, and extract whatever knowledge that you can from that, and then proceed.

So if we look at the existing literature at the time -- actually, before the time -- Steve Byrn's book, which is sort of a seminal reference, of course, had pointed out that if you had compounds that were hydrated, and levothyroxine is a pentahydrate, that desolvation could precede oxidative degradation. So that was known. So I would have hoped that we would have found that.

We had published work classifying the hydrates, the structural basis of hydration in crystal structures. And we found that there were categories, such as channel hydrates, that would allow the egress and ingress of water, not at will but relatively facilely, depending on the structure.

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If you look at the structure -- I don't know how well you can see this in the light, but -- so this is the chemical -- the crystal structure, I should say. The chemical structure's on your right. The crystal structure shows that this is in fact a channel hydrate, so it can pick up and lose water.

What we also found was that depending on the conditions of dehydration -- there's one of the students from LIU is working on the continuation of this project in the audience actually -- if you dehydrate this under certain conditions, the packing motif, that is, the way the molecules pack in the crystal structure don't change, so that leaves the pathway open, essentially, for small molecules, particularly gases, to infiltrate the crystal structure.

So what you see here is from a publication. And you can see on the left-hand side that in fact, when you don't dehydrate, when you maintain it, fine. You take a crystal and put it on the bench, it's fine. And that's what the curves on the upper

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part of the loss profile show there. If you dehydrate it, even if you keep it at a relatively low temperature, it degrades.

The graph on the lower right does the same sort of a treatment, but now this is with and without oxygen. So what Steve's book said about channel hydrates being able to dehydrate and oxidatively degrade is here. It was known.

So we knew it was an NTI. It was known that it was a very low dose, so that the probability of getting -- even at the same level of degradation, could be a much larger percentage.

It's chemically labile. That was also in the literature. There's a nice thesis from Patel from Cincinnati. You may know that. And processing affected the crystal structure because if you break this up and you dehydrate it, then it's labile. And there are excipient interactions known.

Couple that with the fact that the half-life is 7 days. By the time you titrate your patient, as the doctors at the ACPS used to talk about, it

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could be months before you get to the point where you're stable. Now, go from one generic to another, or from brand to generic or vice versa, and there you have the length of time we're talking about.

So what to teach? The dosage form specs need to be developed early. So you should design your dosage form to meet your specifications, not take the specifications that your dosage form gives you once it's made. I know that sounds illogical, but there you go.

So the development process has to be integrated so you can predict the downstream effects. And we'll skip the rest of this, but suffice to say that orthogonal analytics are critical.

So you really have to have a development based on categories. The data mining and creation of an NTI quality clinical response that is the same as a quality classification can be part of what we're talking about as a knowledge base and knowledge management. I won't go through it, but

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this is an example of the start of this sort of a process.

So the research on integrated product development by category across disciplines is really critical, the example I showed you as well. The support for knowledge base R&D, for formulation design, has to be included like NIH includes the necessity of biostatistics in every application. And finally, development of programs for training and expert support for generic companies and reviewers is a key part of the proposals.

So with that, I'll -- well maybe I won't end. No, that's the last slide, and I'll be glad to entertain questions.

DR. LIONBERGER: Thanks much.

DR. UHL: So again, back to this knowledge management, knowledge base, because I'm still having a hard time wrapping my head around this. So when I look at your third slide where you explain development history, and the development history basically creates the electronic living document. Right? So the development history would

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be the development history that the agency gets in an application from industry?

DR. MORRIS: That's what I'd like to see. I think historically, development histories were not reviewed. And I'm not saying that it has to be -- that's something that's up to you -- but to me it makes perfect sense, yes.

DR. UHL: Okay. I'm just making sure I understand where the data come from.

DR. MORRIS: Yes, yes. Yes. From the development project.

DR. UHL: So in that case, the data would be proprietary to the applicant. Correct?

DR. MORRIS: Correct. Yes.

DR. UHL: So can you walk me through, then, how this becomes something that's publicly available? Intellectually, I understand, or conceptually it can massively increase or improve product development. But how do we translate proprietary data into a kind of pre-competitive public/private partnership type thing?

I'm looking at Ruth who deals in this space

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all the time. But it's yours and NIPTE's proposal, so I'd like to hear how you guys have thought through this because, as you said, the development history is in the application, therefore, it is proprietary. How do we make this a teachable database?

DR. MORRIS: Right. No, no, that's a great question. And there's actually two, or depending on what group we're talking within NIPTE, three approaches.

One is that the development history training is not just -- and I don't mean training in the mundane sense of the word, but I mean the introduction of the concepts that underlie the science that lead to the decisions that are made and the development history is part of it.

So they're training, and it can take the guise, as we did with the PAT guidance under Ajaz's direction, where we would come and work with reviewers and go through the scientific part of it in enough detail so that it shows the integrated nature of the work.

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The second part, though, is that even though you can't -- it's sort of like when I was in industry. My research, my published research, was always one level more fundamental than the actual drug I was working on. Otherwise, they wouldn't let me publish it. And the way I look at it is we do that.

In other words, we take that scientific basis and we take some specific examples, and maybe some of the more complex ones, as Steve said, because this is just an example. This one happens to be an oral dosage form, but it's the same for any dosage form.

So you take these examples and then distill from them this approach that is based on the categories because if you look at part of the problems with the 14 dissolution specifications, for example, part of that is because we're trying to fit too many things into the same category. So there's going to have to be more granularity.

Then that gets committed not just to training one-on-one, but gets committed to the

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database. PharmaHUB is, and the hub system in general -- the one at Purdue, at least, was -- it's all NSF-funded, I guess, and therefore it's public. It's secure.

We can have a section of that that is password restricted to FDA accessibility, for example. But then the distilled part of that, the categorical treatment of the individual types of dosage, or of APIs and dosage forms, can be included for public dissemination. So that's the sort of two or three layers that we're talking about.

Right now, if you go to pharmaHUB, and I don't have the link on my slide but I'll include it and send it so it can be put up on the web, you can take a course in crystallography. I mean, you can just start clicking and you can learn -- and, now, when I say crystallography, I don't mean crystallography like what's sodium chloride. I mean, Dave Morrichder [ph], who is one of our post-docs, developed molecular crystallography for drug substances. So it's very specific, so you

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don't have to go through three years of mathematics to be able to understand it.

In this, I would see something much more akin to a searchable, like the FDA, website where you can put in a compound and find out what category it fits in if it's existing, particularly for generics. But you can also do it by category. You should be able to search by structure, and then dosage form types.

So that's about as far as we've gotten. So I'm not saying we have the answers, but that's the idea. So it's really interactive. And in there, in the pharmaHUB too, the third tier is that we did ontological modeling. When I say "we," I mean the engineers did it and I helped them with the subject matter.

So there's actually a database -- sorry, there's actually a program. I can't remember what -- it's an unfortunate acronym. It's POPE, but no offense was intended -- which is the Purdue ontology system to be able to say, okay, for an immediate-release, solid, oral dosage form, here's

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the decision tree and the ontology that leads you to a good formulation. It'll be a higher hurdle for the more complex dosage forms, but certainly doable. Sorry.

DR. UHL: All right. Thank you. I would just say -- as an FDA employee, I can say this -- I hope whenever this becomes something, that is more or better searchable than the FDA website.

DR. MORRIS: Yes. Well, I didn't want to put too fine a point on it, but yes.

DR. LIONBERGER: Thanks very much, Ken.

DR. MORRIS: Thank you.

DR. LIONBERGER: So our next speaker is Eric Munson from University of Kentucky, also representing NIPTE.

Presentation – Eric Munson

DR. MUNSON: So I want to thank the FDA for giving me the opportunity to talk with you about analytical characterization. You've already had a few lead-ins from the three speakers before as well.

So I do have to put up a disclosure. I

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actually am partial owner of a company that provides services to the pharmaceutical industry, but I'm not going to be talking about any of that at this time.

So what I remember from last year's GDUFA meeting was -- I believe it was Dr. Lionberger who actually said this, and I think he repeated it again today, so that supports that -- is that the only difference between an innovative product and the generic formulation, or generic product, is the formulation. So that really stuck in my mind.

One of the things I decided to do is to figure out, how can we take that aspect and really use analytical characterization as a way of improving not only the product performance -- because that's one of the things that clearly has been an emphasis, looking at things like the in vitro composition, the dissolution properties and bioequivalence -- but then getting back and analyzing the product.

The challenge has always been that analyzing the product has oftentimes meant analyzing maybe

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the ingredients, certainly the drug's excipients, but also, then, are there ways in which we can look at the processes? What happens during the process that maybe changes an excipient? And I'll get into that in a little bit greater detail here.

So the idea is to actually translate what you learn from a formulation standpoint. So you have all these ingredients. You figure out not only see what are the drug substances that are there, but also then looking at the excipients, variability that exists, and then look at the drug product in much greater detail than what we currently do right now.

But probably more importantly, try to understand what interactions occur between the drug substance and excipients in the drug product, and see what impacts those have upon the physical properties.

So certainly, for example, we look at polymorphism in the drug substance, but it's actually quite rare that we spend a lot of time looking at polymorphism in the drug product. Also

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try and understand physical and chemical stability aspects.

So in other words, what's the propensity for a drug to degrade once it gets into a formulation, which was actually one of the bases for one of our NIPTE projects on looking at the stability of gabapentin. And we were actually able to predict some of the stability properties based upon how the material was changed during processing.

Fundamentally, once again, what we wanted to be able to do is to take the information that we'd learned on the drug substance and the drug product and translate that into a functional property, once again disintegration, dissolution, and the bioequivalence.

So what I'm going to focus on for the rest of the talk is simply excipient variability. And that just so happens to be one of the topics I'm going to focus on, but that being said, there's a whole range of different ways in which we can look at drug product.

So this came from a presentation that was

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given by someone from the FDA, where essentially risk reduction opportunities, there were two very common causes that were listed. One is deficient facilities and processes, and essentially that came down to humans, and then ingredient variability, so with excipients.

So this is certainly something that will be addressed in a few other talks later today. I know certainly that an organization like IPEC is interested in excipient variability, or the lack of excipient variability, and trying to show whether excipients are equivalent. But certainly there have been recalls due to excipient variability.

A lot of these happen to be due to things like codeine, but fundamentally, what they amount to is that you end up with a failed dissolution specification because an excipient may have been changed to a different vendor. Even the natural variation that comes based upon the time at which a natural excipient was harvested can potentially have an impact.

So I want to highlight one particular case.

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If you're not familiar with magnesium stearate, you probably should be. It's one of the most commonly used excipients used in oral dosage forms. It's also a very complicated excipient, naturally derived.

Even though it's called magnesium stearate, in order to be called magnesium stearate it just has to be 40 percent stearate by composition and 90 percent stearate and palmitate. And then you can have any sort of range of other fatty acids that can exist.

What's shown here on the left is the solid-state NMR spectrum of three different magnesium stearate samples that we obtained. And this is showing the carbonyl region. And essentially, what I want to highlight here is the fact that when you're looking at this, there are quite large variations.

The top one represents a disordered form of magnesium stearate. The middle one represents a mixture of, actually, a monohydrate and a dihydrate form of magnesium stearate. And then the bottom

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one represents a monohydrate form. And then you have the corresponding differential scan calorimetry data up on the top, and then the corresponding thermographic metric analysis.

A couple of points is that if you look at, for example, the top one there, it has a very different DSC thermogram. So this the top one. And maybe I'll show over here. You can see the top one there has a very different DSC thermogram than does the third one.

Yet if you look at the water contents, they're essentially -- the amount of water that's lost is basically the same. They come off with different points in the TGA, but they are very different. So the question is -- we can certainly see that there are differences.

One of the challenges that you have when you're dealing with magnesium stearate is how to actually characterize it inside of a formulation. And the challenge is that the bottom here represents just an NMR spectrum of magnesium stearate, and the area that's shown here in the box

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on the left, you can see that that represents magnesium stearate in this particular form, which is very crystalline.

But when you put it into a formulation, it's practically impossible to see that. So how do you see a material that's present at 1 percent of formulation, and especially study it scientifically?

Our approach has been to actually make our own magnesium stearate. What we do is we C13 label it. And the advantage of C13 labeling is that a signal that was present at only 1 percent by natural abundance now is present at 100 percent. So it's very easy for us to actually identify the form of magnesium stearate that's present in this sample.

This is one of our very first attempts, where we started off with a mixture of a trihydrate, a monohydrate, and a dihydrate. And what we see is that as the material is blended, the trihydrate basically disappears, is converted to monohydrate. The dihydrate also disappears as

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well.

So there's definitely form changes that occur in the magnesium stearate as you do the blending process. So we can use this as an analytical technique to start to really fundamentally understand what happens to magnesium stearate inside of a formulation.

Now the issue is, of course, does this really matter? So the other thing that we're working on in the laboratory is trying to do the correlation of the dissolution data back to what we can identify as the change in the NMR.

You can just see here simply very similar changes, or you can see that magnesium stearate, depending upon how it's mixed -- this is hand mixing so it's quite variable -- but you can see that it does have a pretty significant impact upon the dissolution.

One of the things that we did is then we actually tried to do very consistent, relatively mild mixing. And you can definitely see here the difference between the monohydrate form and the

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trihydrate, the net result being that there are considerable differences in terms of -- well, there are differences between the monohydrate and the dihydrate in terms of how it impacts the solution. And we've done this for a number of different cases, looking in this particular case that the trihydrate always comes out last.

Interestingly, the disordered form, which is one of the things that we would have thought would have been coating the particles the most, actually didn't seem to do that. And that was quite strange for us. But trying to understand the nature of, as you go from one magnesium stearate source to another, which is something especially in the generic industry, could be a very big deal How do you deal with that? So we can see once again another example of the impact upon comparing the trihydrate versus the dihydrate and the monohydrate.

So what I'd like to do is to summarize. What does this mean? So fundamentally, it comes down to characterizing not just the performance,

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and there's a lot of impact on the performance, but also the product. And I think that there is a lot of emphasis, and I've seen that a lot, in the presentations that have been given today. So what it really amounts to is doing that advanced analytical characterization of dosage forms using the variety of analytical techniques that are available to you.

The concept is really to understand the complex dosage form, so really understand not just what went into it, but after it's made, how is it put together. And then convert this into a knowledge base that's accessible. So, for example, we talk about the excipients database, which contains either the quantities of excipients, but doesn't really address things like excipient variability.

Then the third thing is to translate that through to reviewers through an education process. And please, please, ask me about the education process because I would like to provide a little bit more detail as well on that.

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Fundamentally, you can see at the bottom, what do we want to have the FDA get out of this? And what we really need to do is to say, okay, when you have an analytical approach, what are the different techniques that we'll give you to be able to tell you what do you have inside of a product?

Then how do you integrate this into that design development space? And then how do you validate it? So in other words, especially when you come up with some of these newer methods, how are you able to validate them?

Another question is that how well do these work across the dosage forms? So certainly we saw a lot of different dosage forms that potentially, for example, could be characterized using solid-state NMR spectroscopy. A lot of the ones that were presented in the first talk of today could certainly be studied that way.

Then fundamentally, when you have this information, how do you translate that into QC testing. Okay? And then when you have a root cause investigation associated with something that

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fails, how do you take these approaches and be able to solve your problem?

With that, I'll be happy to answer any questions you have.

DR. LIONBERGER: Thanks much.

DR. BUHSE: So you and several before talked about education of reviewers. But it also seems that there needs to be maybe, potentially, a fundamental education of drug developers as well in terms of if they develop it, or if they ask the right questions up front, before they start, even --

DR. MUNSON: Yes.

DR. BUHSE: -- potentially, then we're not put in a position where we have to try to figure out that they used the wrong mix, data area, or whatever. So it seems like the education needs to start pretty far back in the chain, even before we see a drug.

Is there a way you can infiltrate your knowledge, et cetera, to especially the generic industry, a lot of which often are not located in

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this country, potentially, et cetera, to increase knowledge such as that what you showed today?
DR. MUNSON: Okay. Yes. So certainly that is exactly what we want to do. So one of the things that we actually talked about at dinner last night was establishing a series of short courses, maybe a one-day course that addresses various topics, analytics, unit operations, et cetera, where we would come in and provide roughly 12 to 14 of these courses on a rotating basis.
So one or two professors would come in, provide a one-day short course to the FDA. And at the end of that, we'd end up with a certificate that you've accomplished this. And then we would translate that into something that maybe gets to -- and more advanced. So in other words, once you've done this first step, you may get into a second step, maybe into advanced formulation.
One of the things we want to do is to take that knowledge, then, and translate that into an industry program where we would also do these types of education events at industry. And we're

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actually currently working on doing that with generics, I'll say, in another country. So we are doing that translational process.
But that's one of the concepts that we're thinking about, is also giving the opportunities for the reviewers and the inspectors to come in and talk directly to, I'll say, the content experts, the faculty, so that we are onsite and can answer questions, and can get into a little bit of a dialogue without getting into very specific issues associated with a particular document.
DR. BUHSE: Can I just follow up on that a little bit? Because when Ajaz presented, Ajaz said that NIPTE already gets funding from FDA. Is that correct?
DR. HUSSAIN: (Nods affirmatively.)
DR. BUHSE: Thank you, Ajaz, for nodding yes, since you're not on the microphone.
So in order to do those type of training that you guys are talking about, it's not currently incorporated into your annual strategic plan with the current budget that you have. Is that what

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you're --
DR. MORRIS: That's true. And once again, certainly one of the things that we'd like to be able to do is to work with the FDA. From our perspective, what we want to be able to do is also talk to people at the FDA, especially as individual faculty members coming and telling you about what we know. And from our perspective, that's -- we can talk about the relative cost of it, but we don't want to do it for a large cost.
DR. UHL: Right.
DR. MUNSON: What we'd especially like to do is to have the opportunity to talk to the FDA.
DR. UHL: So I know that there are several speakers coming up that represent industry, in the generic trade industry. So since the GDUFA research, regulatory research program is essentially funded through GDUFA funds, maybe you have some speculation on how the generic industry might feel about this. Because that's -- Rob laid out the program already. It's about $20 million a year.

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DR. MUNSON: Yes.
DR. UHL: So I don't know if the generic companies who are going to come up and present want to comment on how they'd like to see these monies spent, or if you guys want to think about it and submit to the docket. But it's a limited pool. How do we best use it to drive the outcomes that we really need from a generic product development standpoint?
DR. MUNSON: Yes. Well, certainly one of the things I remember -- and once again this is all speculation because I'm not going to present that I represent the generic industry -- however, we do know that they are very interested in education. They have approached NIPTE for education. So we know that that is a very important component.
In terms of specific topics, I've talked to people from GPhA about things like excipient variability, and we know that that's a very big topic for them as well. So there are several ways in which we -- we feel like we're trying to address the questions that I know people from the generic

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industry do care about. And that is one of the things that we're trying to address.

Now, once again, I can't speak for the generic industry per se. But I think that these are topics that they care about. And certainly education, I think, is something that they would also be very interested in, especially because if anything, that helps them get through the review process, so that the FDA people and the people in the generic industry understand that they're getting the same level of education, that that would actually be quite beneficial for them going through the review process.

DR. LIONBERGER: All right. Thanks very much, Ken.

So we'll move on to our next speaker. It's Professor Amy Barton Pai from the Albany College of Pharmacy and Health Science.

Presentation – Amy Barton Pai

DR. BARTON PAI: Good afternoon. I just wanted to extend my thanks to the FDA OGD for giving me this opportunity to really talk to you

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about challenges relevant to bioequivalence assessment with IV iron formulations.

My research program focuses on differential toxicity profiles of IV iron formulations, but in addition, I am a nephrology-trained clinical pharmacist, and I've worked in the dialysis population for more than 20 years. And this population is a ubiquitous user of these agents, so it is a very relevant topic.

I have nothing to disclose.

As Dr. Lionberger really teed up nicely in his opening remarks, IV iron formulations are complex products in that they are colloidal suspensions of nanoparticles. This is something that I don't think most clinicians who use these products appreciate, so they do have unique challenges.

Most of our experience with these products is actually gleaned from the global market, where there are many generic iron sucrose products available globally. The regulatory oversight for these products is variable. And typically,

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countries that utilize these generics have mandated switches.

What we do know is that some animal models have pretty universally shown increased oxidative stress induction and higher tissue deposition of iron with generic formulations of iron sucrose compared the reference listed products.

Clinical observational studies are also accumulating in the literature as these mandated switches have occurred. And they have demonstrated reduced efficacy as well as increased adverse event profiles related to the generic products versus the RLDs. Notably, these differential safety and adverse event profiles have been mechanistically linked to direct release of labile iron from these formulations.

So through some UO1 funding, our group was able to really engage in a systematic approach to try to better predict serum non-transferring-bound iron, which is also known as labile iron, from IV iron formulations.

Our project essentially looked in tandem at

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studying a multiplicity of different assays to measure labile iron through chelatable and redox active mechanisms. We then studied all of these assays in vitro to determine possible applicability for measurement in vitro, and then subsequently chose candidate assays to measure labile iron release in vivo.

The products we studied were all of the currently available reference listed drugs at the time this study was initiated, as well as the only approved US generic, which is sodium ferric gluconate complex.

After the data from the in vitro and in vivo pieces were accumulated, we sought to see if some of these data could at least potentially begin to inform an in vitro to in vivo correlation model. So I'll walk you through a little bit of this project.

Essentially, at the very beginning, we exposed all of the products to the typical battery of physical-chemical characterization techniques that are used in the nanoparticle space. The ideal

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here is obviously that physical-chemical characterization is able to reliably identify differences between the reference listed drug and the generic, and that we could potentially be able to use some of these data to predict labile iron release.

However, the dilemma is, as other speakers have alluded to today, that the formulation complexity and variable stability profiles of these formulations create very unique challenges in the reliability and reproducibility of PCC.

So just to share an illustrative example of that, when we looked at different particle size, or polydispersity, we first did a field flow fraction followed by quasi-elastic light scattering. The red dotted line here would represent monodispersity.

The important notation in this graphic is that sodium ferrate gluconate complex was able to be characterized by this technique, but Ferrlecit, the reference listed drug, was unstable to the washing step in the field flow fraction analysis.

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So we essentially are not able to compare these compounds.

We then again sought to evaluate a number of different labile iron assays. Notably, the first assay listed here is the bleomycin-detectable iron assay. This is currently an assay that is referenced in the draft guidance for sodium ferrate gluconate complex. The other redox active and chelatable iron assays are noted here.

But importantly, these first three are really not applicable at all for use in in vitro work due to apparent interference of the actual agents with the assay. And notably also with bleomycin-detectable iron, it has other practical limitations. Notably, it's used as a chemotherapeutic agent in its assay technique, and also requires -- is very highly subject to human error. I'll leave it at that.

The assay we did identify that seemed to work quite well in vitro was an HPLC desferrioxamine assay. And this assay actually also had an interesting kinetic binding effect of

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the DFO to the labile iron that could potentially be exploited for possible bioequivalence analyses.

These are data from our in vitro work. And essentially, we diluted compounds in saline in a biorelevant matrix, which is rat serum. And all concentrations, all final concentrations, were essentially the predicted Cmax of a 40 milligram per kilogram dose.

Notably, from this graphic here, it's important to note that all the compounds did have lower stability in saline, which is well-known. And you can see there is some slight differences between the Ferrlecit and the sodium ferrate gluconate.

I'd also ask you to note the bottom product, which is an investigational product from GE Global Healthcare. It's a pegylated iron product and was meant to represent an out-of-class assessment. But if you note, the stability in rat serum is quite stable and does not release tremendous amounts of labile iron. But there is a difference in vivo.

So moving on, this is our in vivo

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concentration time profiles in healthy male rats. We developed this PK analysis in a three-step iterative process, which was first dose-finding, followed by an initial PK to optimize sampling times, and final PK analysis.

What you can see from the top panel with the Ferrlecit, the reference listed drug, and the sodium ferric gluconate complex, their concentration time profiles are very similar, in fact, perhaps superimposable. If you note again on the bottom right panel, the GE product actually had the most labile iron release in vivo. So that's in great contrast to what we saw in vitro.

This is an initial PK analysis. So in this analysis, clearance and volume are actually a ratio over the bioavailability, which is the bioavailability of labile iron release from the compound, which is unknown. So these are relative clearances and relative volumes.

We evaluated essentially a release constant, which we called KR. And this represents the rate of direct release of labile iron from the iron

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carbohydrate complex. So what you can see in this analysis relevant to the RLD and generic is that this KR is very similar between the two drugs.

So wrapping up here with what I believe is probably still needed in this arena, clearly we need further evaluation of physical-chemical characterization limitations for inter-product comparison. This could even be as granular as instrumentation that's used between manufacturers.

We certainly need to study additional formulations, both in vitro and in vivo. Again, this represented just a single generic IV iron formulation. So many more need to be studied, whether that's in the global marketplace or handled domestically.

Lot-to-lot variations is another issue that has presented itself on the global market, with differences in labile iron release between lots. It will be important to more clearly define the optimal assay for labile iron measurement, both in vitro and in vivo. And essentially, leading to further analyses, to possibly develop stronger and

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more predictive models for labile iron release that obviate the need for in vivo work.

Finally, as these products start to emerge on the marketplace, as a clinician I believe it's really important to have close marketing surveillance of these products, as well as assessing usage patterns.

Ultimately, working in this space for the past 20 years, I can say that clinicians who use IV iron products are not aware of the complexity of these formulations, and should be educated on the complexity and the unique challenges that exist.

With that, I'll conclude, and I'm happy to take any questions.

DR. LIONBERGER: So with respect to your comment on -- there's multiple currently approved products. Do clinicians think that they are different, or do they interchange them? You know, is there a sense that there are differences between the approved different RLDs or not?

DR. BARTON PAI: I would say the clinician perceives the dominant differences as

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immunogenicity, and their ability to give a larger dose in a single infusion. But as far as physical-chemical characteristics, they, I would say, are largely unaware. They dose iron. It's all based on elemental iron, so their switching is based on safety profiles as well as ease of administration when giving larger doses in more outpatient settings.

DR. CONNER: The one generic that you had in your list, what was the RLD for that, the reference listed drug?

DR. BARTON PAI: Ferrlecit.

DR. CONNER: Ferrlecit. So the real comparison, or test of your methods, is comparing that generic to Ferrlecit?

DR. BARTON PAI: That's right.

DR. CONNER: How well does that do in your testing?

DR. BARTON PAI: So again, just to recap the data here, in many of the physical-chemical characterization pieces, there were differences between the RLD and the generic, possibly because

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of, again different steps in the analytic process. The in vitro piece, it looked like the brand had more labile iron release. However, in vivo, again those profiles were very similar.

DR. UHL: Could you go back one slide? Same question I asked earlier this morning. So you've got seven potential ideas. We have about $20 million on an annual basis. So could you tell me what your number one priority would be, especially as it relates to this aspect of IV iron therapy?

DR. BARTON PAI: I think this ties in certainly to the confidence in substitution. So in an incremental way, I would say the predominant piece is elucidating these physical-chemical characterization limitations because that's inherent in the guidance right now, and following up with additional in vitro and in vivo study of additional generic formulations.

DR. LIONBERGER: Thanks very much.

So our next speaker is Professor Diane Burgess from the University of Connecticut.

Presentation – Diane Burgess

DR. BURGESS: Got to be able to walk fast here. Okay, good afternoon. Thank you for the invitation. I'm very pleased to be here. Probably need my glasses to work out how to figure this.

So what we've been doing in one of the grants that we have is with microspheres. I'm presenting that work because it's furthest along. We've been developing Q1/Q2 microsphere formulations that we're deliberately doing with minor manufacturing changes, very minor, to see what are the critical manufacturing changes that can have an effect on the product performance.

So we chose, first of all, Risperdal Consta, but we are working on other drugs as well. So we chose Risperdal Consta and we made very small changes with, as you can see here, the -- so we used different solvents, a DSM and ethyl acetate. And we also made other slight changes in the method of mixing and the method of sieving.

So we had drug loading very similar. And this slide had some of the physical-chemical

characteristics -- the particle size, not too much differences in particle size, a little bit with the difference in the sieving and with the difference in the mixing here.

But what I really want to point out here is the difference in the porosity because with the ethyl acetate, we got much more porous microspheres compared to with the DCM. This was also more similar to the reference listed drug product.

So in moving on, we did our in vitro release testing. And the typically used method is a sample and separate method for microspheres, as reported in the literature. But in our lab, we've developed another method several years back, which is an apparatus 4, where we put the microspheres between the glass beads and hold them in the apparatus 4 flow-through cell. The advantage of this method is you get around aggregation problems as well as floating problems that can happen with the sample and separate and even USP 2 apparatus.

This is results with the sample and separate. And we found that we did have some

aggregation, and we were able to resolve some of that by using surfactant for the sample and separate method. So we were able to get a better resolution of our four different microsphere products. This is not with the RLD, but the four that we were making Q1/Q2.

With the apparatus 4, we got -- again, very good differences here were able to show up. And one thing I wanted to point out is that with the more porous microspheres, the two that were made with ethyl acetate, with either method we didn't see very much burst release.

That method of manufacturing had eliminated some of the burst release, whereas with the other method, where it was less porous, we were getting burst release. So that was one significant difference, as well as the slight differences in the rates that we can see here.

We then went on to do in vivo work that we did in rabbits. So this is an IVIVC, as such, with rabbit data. And we used the Loo-Riegelman method to deconvolute the data. So this on the top here

is our rabbit data. So our in vivo release profile with a rabbit for Risperdal Consta, this is the RLD, and here we have the deconvoluted.

I'm showing the RLD here because we can, from the literature, get the human data from the literature -- for the RLD, obviously not for the formulations we made. And we can see here we've deconvoluted this data so there is very good similarities but inter-species difference, as you'll probably notice here, much, much faster in the rabbit.

In our rabbit model, we used the hind leg, whereas the human it's into the gluteus maximus. Big differences in fat content and also in the vascularization. Vascularization is probably the bigger difference, where you're going to get more ready dissolution, larger volume there. And the other difference is, of course, is the metabolism in the rabbits. We did do the risperidone. We looked at risperidone in vivo, and there are differences in the metabolism.

So looking at the four formulations that we

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made, the big difference here is the two with the burst release. That's obviously going to be your Cmax and Tmax, whereas the ones without the burst release, their Cmax and Tmax is -- so is shifted, obviously. So that was one big difference here.

But we went on to do our deconvolution. And our four formulations are to the left, and the Risperdal is the red one to the right. So what we did is we used three of our formulations to make an IVIVC in order to predict the fourth formulation, so 1, 2 and 3 to predict 4, or 2, 3, 4 to predict 1, and so on. So this is our IVIVC for 4/3 combinations.

Then we used this to predict the in vivo release for the fourth one, and you see here we're getting really very, very good prediction. So this is for a complex product. Microsphere is one of the most complex, especially when you've got the three phases of the burst, the lag phase and then the secondary release profile. So we were very pleased with this.

We also used these four to predict the RLD.

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And again, you'll see really, really good prediction. And based on the USP 4 apparatus method, we got really excellent prediction, the PE of 10 percent or less. When we did use the sample and separate method, which we had shown wasn't as good an in vitro release method, at least for these microspheres, then we didn't get a good IVIVC. It was basically inconclusive at best.

So we're now working, or we've just completed a study also with naltrexone. And this is two-phase. This doesn't really have burst release, but we've got three formulations. And we've shown excellent, again, IVIVC for these three formulations for the naltrexone as well. And we're now working on a peptide formulation.

So I think that, to quote from Ajaz, that I think we're moving from the microspheres, from just being a complex dosage form, to a complicated one, if I understood what Ajaz was saying correctly; that now we're really starting to understand the physical-chemical properties that are important, and we are able to develop an IVIVC so we could be

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able to -- in the future, obviously with more information and really, really good physical-chemical characterization, we could be able to move towards at least some looking at bioequivalence for this type of product.

Another product that I think we haven't worked on yet but I think we should is the long-acting suspensions because I think this is a kind of low=hanging fruit, relatively easier formulation, from the formulation and manufacturing perspective. So I think this would be a good one to tackle next.

The one that Chetan mentioned, the ophthalmic, we are doing some work on the ophthalmic area. And there I think we can get a very good in vitro release method, definitely, that could discriminate between manufacturing differences. But to move towards an IVIVC for something like ophthalmic, I think, would be, as Chetan pointed out, very difficult. So some of the physical-chemical characteristics might be more important or at least as important there.

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The last thing I wanted to say was talk about the in vitro and in vivo stability issues with these complex products. With the microspheres, for example, I'm familiar, and some of the other PLG formulations. We get interaction with the drug such as risperidone and naltrexone. Even with the peptide drugs, we've got interactions. And with the peptides, it could be even more complicated because of the potential immunogenicity problem.

These interactions can occur during manufacturing; with different manufacturing, methods may get more or less of the interactions with these drugs, so more or less possibility for immunogenicity, and so on. And how you manufacture them can also change how they may behave during shelf life storage because of different porosity and so on with the humidity conditions.

That also can impact on those changes occurring in vivo when you're looking at some of these products, or not just weeks, but months and even years, in the body in that human environment

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with porosity and so on. So I think that this is another area that I think we need to have some focus on.

So just to acknowledge the funding, particularly the FDA funding there in the middle. And my research group, and to the left of me is Jie Shen. She did a lot of the work I presented today. Also, Janki to the left of Jie. And then this is some of the rest of my group. So thank you.

DR. LIONBERGER: Thank you. So one of the challenges in these products is that since they're long-acting, you have to do very long PK studies to show bioequivalence. So how far are we, or what new data would we need, potentially, to support a waiver of a bioequivalence study?

DR. BURGESS: Well, I think with the microspheres, I can speak. I think we're getting very close to really understanding what are maybe the Q3 type of things, Something like the porosity would be a Q3 property, so to understand those properties.

There are a few products that we could still

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do and attempt to do IVIVC. And we've been able to develop what I think are very robust IVIVCs for two products now.

So I think that we're really moving in that direction because we're able to use those two, for example, to predict the RLD. And even with two of those having a burst release and two not having a burst release, we still got pretty good prediction.

So I'm confident that we're moving in that direction. And with more robust -- if the generic companies do a very good physical-chemical analysis of their product, I think if they have a good portfolio with that I think we could be able to move forward with that for them.

DR. LIONBERGER: All right. Thank you very much.

DR. BURGESS: Thank you.

DR. LIONBERGER: So our next speaker is David Gaugh, representing GPhA.

Presentation - David Gaugh

DR. GAUGH: Thank you, Rob, and good afternoon, panel. And thank you for holding this

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public meeting. We greatly appreciate it. As one of the key stakeholders in the GDUFA realm, if you will, this is very important and near and dear to our hearts of the generic industry. So thank you for holding this public meeting.

I think at least the panel, I know, knows all about GPhA, so I'm not going to go through this. And I believe these are going to be made public, so the rest of the audience will be able to see them. But you can read them as we go along.

Just a list of our members. So we represent approximately 35 full members and approximately 45 associate members. So a large spectrum of the generic pharmaceutical industry is represented by GPhA.

If you take not this slide and the numbers that are on the slide, over 90 percent of the products manufactured and sold for use in the United States is represented by the GPhA companies. So if you have questions about generics. we can get that message out pretty readily to most of the constituents.

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Statement of mission. I know that there isn't a specific mission statement that the regulatory science team has, but this is coming from an article and an interview that Dr. Lionberger had last year.

We think it's very important to make safe and effective generic drugs available to the American public by ensuring that OGD standards, as reflected in review guidance and communication to sponsors and the public, continue to be based on the best currently available science and results of regulatory science research. So we think that's a very important tenet to keep at hand.

If you look at the GDUFA goals letter, which was developed back in 2012, "FDA will convene a working group and consider suggestions from industry and other stakeholders to develop an annual list of regulatory science initiatives for review by CDER director."

Again, we think very important. This public meeting is one of those opportunities for a working group, but as you'll see as I go through my slides,

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we think there's other opportunities for working groups and collaboration that we would like to see the agency take on going forward.

GPhA and other stakeholders began dialogues with FDA to explore how best to broaden industry's input into the development process of the annual list. But to date, no action plans that we presented have been taken up, so we hope that these working groups will help us get to that point.

While GPhA is supportive of the regulatory science initiative, payers into the GDUFA program want more input, and one public hearing is not what we consider to be enough. So therefore, we're asking for more working groups going forward.

So what I'm going to do is not address specific products per se, but opportunities for input, if you will, and consideration. So increased collaboration to identify the annual regulatory science priorities. Increased transparency and involvement with the decision-making process for the user fees that are used.

User fee funding of studies and projects to

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be distributed in terms of short, intermediate, and long-term goals so the generic industry can benefit from the knowledge gained from the results of these studies, projects, in real time as much as is possible. And again, we've already talked about the working groups.

From a transparency standpoint, FDA to improve transparency and communication regarding how it determines the focus of the studies and projects, determines the scope of those studies and projects, and their benefit.

Determines how the results of the studies and projects are interpreted and utilized by the FDA. And determines the overall impact of the science and regulatory initiative program that has had an increase in patient access to generic medicines.

So there were some specific points that Dr. Lionberger and team put out for consideration, and so here are some suggestions that we think would be very important. And the user fee monies that are provided, we think, would benefit greatly

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from this as well.

Opportunities for scientific or technical advancements: First, a discussion and expectations on nanotherapy and characterization. Opportunities to have scientific exchanges between industry and FDA in the form of workshops. I think I've said that a few times already.

Number 2, innovative approaches to pre-approval development of generic drugs, so discussions and expectations on in vivo and in vitro correlation methods for low-dose concentration products such as otics, ophthalmics, long acting injectables, and auto injectors.

Discussions and expectations on product subject to clinical endpoint studies in which the primary endpoint is difficult to measure and/or difficult to distinguish.

Discussions around developing a premise with well-defined in vitro methodologies to replace the need for clinical endpoint studies is another consideration. Discuss and expectations on setting clinical relevant specifications. And discussions

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and expectations on qualifications of dissolution apparatus and methods.

Third, innovation in scientific approaches to evaluating the therapeutic equivalence of generic drug products throughout their life cycle, so the narrow therapeutic index products and drug device combination products.

Four, the high-impact public health issues involving generic drugs that can be addressed by prioritizing allocations for the fiscal year 2017 funding. Timely guidance developed for high impact generic products, first generics, NCE-1 products, and very importantly, complex products.

Number 5, identification of specific issues related to generic drug products or scientific recommendations and/or clarifications are needed. So discussions and expectations of long-acting microparticles of aseptic processing on characterization of peptides and iron products; on the characterization needed to show similarity for devices for combination products.

The risk analysis for delaminating glass

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vials and potential testing specifications for this delamination. Extractables, leachables for all dosage forms, sterile and non-sterile. Expectations on generic abuse deterrent formulation products on a USP Chapter 232, Elemental Impurities.

On adhesions for transdermal products, on guidance to address the limitations with current scoring scales and statistical methodology for assessing non-inferiority and adhesion and irritations for transdermal products.

Finally, under number five is the evaluation of the approach to safety evaluation for certain types of commonly-used excipients.

Number 6, strategies for enhancing quality and the equivalent risk management during generic drug product development. Assessment of the comprehensive safety risk for food additives in oral drug products.

So additional points to consider besides the six that you provided to us and we tried to give you some clarity on response; those are not deep

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dives, as you can tell, but we would love to be able to, as you develop programs, get into those working groups that we talked about before.

But one such area was the creation of new tools by the FDA for use in assessing the safety, effectiveness, quality, and performance of generic drug products. We think that's critically important, and I've heard that already two or three times today.

The scope of this request was to include, but not limited to, the FDA addressing the concerns with regards to the reviewer consistency, updating, improving, and enhancing the IID, as well as improving the quality of the submissions that we're talking about.

Industry's ask on the IID was to ensure data reliability and the ability of industry and FDA to make consistent and sound regulatory decisions, improving quality standards for drug development, and encouraging and promoting innovation.

So in conclusion, we look forward to working closely with the FDA and other industry

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stakeholders, besides just the generic industry, in order to develop a comprehensive and meaningful 2017 regulatory science initiative program.

Thank you, and happy to take any questions.

DR. LIONBERGER: Thank you, David.

DR. BOAM: Thank you, David. I was just going to ask, and since I realize this is probably a compilation of recommendations from your members, would just welcome a follow-up to the docket. But one of the items under number 5 you asked for was discussion expectations on aseptic processing.

It would be useful to know what about our current guidance on aseptic processing is lacking. If there are certain aspects of that you'd like us to expand upon, or if there's certain things that are either not covered or not covered clearly in that guidance, we would certainly welcome that input.

DR. GAUGH: So no, we're going to start working groups on these ourselves. So whether they're taken up by the agency or not, we'll have working groups on them. So a lot of things have

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been changing over the past few years on aseptic processing, and we want to make sure that we have a clear understanding as the agency moves along the spectrum of what aseptic processing is acceptable and what is not. So we can come back with more details.

DR. BUHSE: Thank you. These are many specific targeted recommendations. But I want to take a step back and ask about some of the terms you used. I understand that the members in GPhA are seeking more input into the development of the regulatory science initiative.

When you make a request for a discussion and expectations, I think I understand the expectations point. But with respect to the discussion, are your members looking for an ability to speak with FDA as we develop these scientific understandings, or develop the scientific regulatory agenda to address those? Or are you referencing more discussion once we have developed these with individual companies in a one-on-one way or iterative way? Can you just talk a little bit more

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about what you meant by the discussion request?
DR. GAUGH: Sure. And the answer to your question is both. So at the moment, we are doing some of that, and when I say we, the agency, GPhA, and the appointed study universities, whatever they might be.
So once the program has been assigned and the program sponsor starts working on that project, they do reach out to either industry companies or to GPhA to have discussions and talk through how that process is going to work.
I think it's very helpful because in some cases, the definition that they have -- the study they've taken on maybe is not completely understood by the group that's taking it on.
So if it's utilization of products, for example, is it utilization of products that are currently on the market or is it utilization of products that -- not currently on the market, they are currently on the market. But in some cases the uptake of products is much higher than others.
I didn't go through the slide, but generics

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are 88-percent of the utilization. So if you're looking at a study that would be about increasing utilization, it's going to be pretty hard to increase that global utilization.
But if you're looking at specific products, where in many drug categories -- as you know, products are not utilized at 88-percent if they are generic necessarily. They may be lower, in the 10 or 15 percent range.
So having discussions with those study groups around that helps redefine that focus. So that's once assigned. But we would also like to have discussions as you're going into the assigning to make sure that the definition of where you're going with the project and where we might think it should go could have that discussion. And it might help redefine it. It might not, but we think it might be helpful.
DR. UHL: David, thank you for coming and thank you for your sharing of your members' requests or input to the agency. On your second-to-last slide, you mentioned new tools, creation of

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new tools by the FDA. Was there any particular input from your member companies about what kinds of tools that would be helpful or valuable?
DR. GAUGH: No. We don't yet. So that's part of --
DR. UHL: Because I've got a big toolkit.
DR. GAUGH: We've got a big toolkit. No, not specifics, but we want to -- again, we're going to do that on our own. We'll get into a working group to help define what that can look like.
DR. UHL: Good. And then you could provide that kind of input to the agency for sure.
DR. GAUGH: Absolutely.
DR. UHL: In some prioritization schema?
DR. GAUGH: Yes.
DR. UHL: Okay. That would be very helpful.
DR. GAUGH: Yes.
DR. UHL: Thank you.
DR. LIONBERGER: Do you have currently different working groups in regulatory science areas where you have participation from broad group of companies in those subgroups? Do have those

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organized? I mean it wasn't --
DR. GAUGH: Yes, we do have.
DR. LIONBERGER: What are the topics that you currently have or people are organized for?
DR. GAUGH: So it depends, if you will, on what we're talking about. In some cases stability was one. That's not what we're here to talk about. Emerging technologies is another. So I know that the FDA is taking up emerging technologies as a working group internally, not necessarily externally. Continuous manufacturing is another one that's been taken up by the agency.
DR. LIONBERGER: I'm asking about groups that the GPhA currently has of industry people.
DR. GAUGH: I'm sorry. I'm saying we have our own industry groups not related to the FDA.
DR. LIONBERGER: On these topics? Okay.
DR. GAUGH: Yes. Those are just two examples. Then we do have industry working groups on continuous manufacturing, emerging technologies, for example. And that also gets back to your question about -- or not yours, I'm sorry,

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Ashley's -- about the aseptic. So we're looking at that as well.

DR. LIONBERGER: We'd encourage, in topics where you have interest from multiple companies, to facilitate forming these groups and having those groups provide very specific recommendations into the docket. If they're prepared this year, get those groups to send in their consensus, things into the docket in particular areas.

DR. GAUGH: Right. Absolutely we will. Yes.

DR. STODART: Thank you. On slide 7, you mention several methods or several areas where we can improve transparency and communication. Do you have any specific suggestions as how we would go about achieving that?

DR. GAUGH: I'm sorry. You said slide 7?

DR. STODART: Slide 7, for transparency and communication.

DR. GAUGH: I'm still having a hard time hearing which one --

DR. STODART: No. On slide 7, you list

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about five different areas in which FDA can improve its transparency and communication. So I was just asking whether there are any specific suggestions you have as how we could go about achieving that.

DR. GAUGH: Again, no. We've just started the working groups. So in the past years, to Rob's point, we haven't had these robust working groups together yet, and so we've just started pulling those together. After conversations that we've had with GDUFA negotiations in the past many months, we realize to get to that point that you're asking about, we need to get these working groups together.

DR. STODART: Thank you.

DR. GAUGH: You're welcome.

DR. CONNER: Yes. There are quite a few points here where you're obviously asking for more input into the regulatory program. But to repeat Cook, who has made this -- and I'll make the request before I make my comment, that you have a rather large list of good ideas here. But only being approximately $20 million, do you have any

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prioritization or do your members have any prioritization?

It folds into the next question. Obviously, even if you look at the list of members you have here, not to mention the other non-GPhA constituents of the generic drugs program, which often have very different interests, how would you, or we, prioritize these things when you have so many constituents of your own with very different priorities and very different opinions about what's important and what's not?

DR. GAUGH: You ask a great herding-the-cats question.

DR. CONNER: Right.

DR. GAUGH: So to answer your question, we do have a large regulatory working group, and we will go through now and work on this and get those priorities there. You're right, there's $20 million that was earmarked out of GDUFA I, but I don't think that necessarily stops the agency from using more than $20 million in the GDUFA dollars or in appropriation dollars.

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So we think there's opportunity for an even broader base of projects and programs to work on. But to your point, we'll come back with a priority list because we know you can't work on all of these that we're listing out, absolutely.

DR. LIONBERGER: All right. Thank you very much, David.

DR. GAUGH: Thank you.

DR. LIONBERGER: So your next speaker is Nikunjkumar Patel from Simcyp.

Presentation – Nikunjkumar Patel

DR. PATEL: Thank you, Rob, for introduction and invitation to present at today's meeting. I think there was a day-long workshop yesterday on this topic which I'm going to speak today, so most of the points I wanted to discuss today were already discussed and debated. But this is a quite interesting and evolving area of research which could help generate product development and assessment.

So for the people who were not here yesterday, and who are not from the field, what the

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PBPK is, PBPK is physiologically based pharmacokinetic modeling. And as you can see, when you talk about pharmacokinetic, there are multiple types of models which are typically used.

Some of them are empirical, like exponential models, some compartmental models. Those type of models are useful when you already have clinical data and you want to see whether that clinical data was obtained from one bucket of blood or one bucket of blood and one bucket of fat, so those kind of analysis.

But when you look at the PBPK, PBPK is basically based on the underlying knowledge of physiology that we have, the current knowledge of physiology, and you try to port out the system by giving a drug product. So you are trying to assess how the drug is going to treat a drug when given in a particular product or a particular formulation.

So it has quite a good predictive power. And you can use prior information, so you can start using it from early development until late stage. And at each stage, you can try to build more and

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more confidence into your model, and finally will have very good confidence so that you can use it to make some critical decisions about product and product changes.

So I think there is a long list of applications where PBPK has been used, and these are from the public literature. And this is not an exhaustive list; there are even more applications. Some of the critical one are an application in quality by design or setting of dissolution specification, establishing IVIVC. This is an important one.

I think there was a quite good amount of interest in pediatric and how to assess them. Maybe PBPK can help to translate adult data to pediatric, or maybe a disease population. Impact of food effect as well as impact of proton pump inhibitor at a gut level drug-drug interaction, what show bioequivalence.

This is another important point I want to discuss today, is that assessing the untested scenarios to fill the gaps in the product

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assessment.

Starting with QbD, so I picked up two examples, but this is not and exhaustive list. There are multiple examples in the literature. So the first one is from the FDA group, so I think this is a nice publication where they put together a framework in which PBPK modeling can fit into a quality by design type of assessment.

There is another recent publication from our group, so I think they set up about, I think, five or six different examples where modeling and simulation can be used to answer or address some of the questions which are typically raised in quality by design paradigm.

Because of the interest of time, I am not expected to go in detail. That's why I put the references. So if you are interested, you can go and have a look in detail.

But when we look at this and some other publications, there are many times they fit parameters because I think the model is not obviously predictive, so you need to add some of

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the known or uncertain parameters.

So the question I have is, basically, when you do a fitting, because these are the complex models, and physiology is so variable and uncertain, maybe you are estimating or fitting a drug and formulation parameter which might be accounting for some uncertainty in the physiology. Maybe your physiology is not right and you are unknowingly estimating a product parameter to represent uncertainty in the physiology.

So in those cases, the question is, what is a qualification criteria? When you fit a parameter, what should be your endpoint? How do you decide whether the parameter you fitted is correct or you are not over-emphasizing on a particular property?

The second question is that -- I think this is another ongoing debate and discussion -- what is a physiology in the PBPK platform? If you look at different platforms, there are sometimes some parameters which are arbitrary. Some of them are assumed.

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So the question is, when you use PBPK, do you need to have reference for physiology which is being used in a platform -- or by a user, because they are obviously modifiable -- so do you have to have a physiology which is scientifically traceable, which is actually linking to a physiological measurement based on our current understanding? Or it can be assumed or arbitrary. If it is assumed or arbitrary, what is your acceptance criteria?

Again, it is basically building upon the previous question. So basically, PBPK is a probabilistic modeling rather than an accurate, or basically like compartmental kind. It is where you have data, you try to explain it. So when it is a probabilistic science, is it all right to just use an average human physiology provided in the platform, or you need to do a population simulation?

I think there was a quite interest in the discussion yesterday on global sensitivity analysis. So that basically says to you that you

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need to account for all the uncertainty in the physiology, as well as variability, to make a decision. So this is another question. I think we need to address all these questions before we can move on to use it as a regulatory submission, too.

Another application is basically translating adult to pediatric data. So I think this is a very recent publication from Jennifer Dressman's group. They developed and validated a formulation, or basically PBPK model, for fluconazole and ketoconazole, and then tried to see if they can translate this information to a children or basically adolescent patient. So I think there was some discussion on ontogenies of enzymes.

So basically, these two drugs have been metabolized by the enzymes, which undergoes significant modification in early ages. And that's why the children dose is relatively higher in terms of milligram per kg as compared to an adult.

Also, the physiology difference is in the gut. If you use the same formulation in adolescent or children population, is it going to behave the

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same under a given physiological condition, et cetera? So probably this type of assessment can be done using PBPK. This was another publication from Rob's group.

The third publication is from AstraZeneca. So what they did is they had an immediate-release formulation and extended-release formulation in adults.

Also, they had assessed the immediate-release formulation in pediatric, but they did not assess, or they did not have clinical data, of XR in pediatric. So they wanted to see whether they can make some projections how this is going to behave in adolescent patients.

So they had an IVIVC established, validated, and accepted for XR formulation in adults. So they tried to translate the IVIVC for children, and tried to make some decision on the dose as well as the expected population variability.

When we talk about pediatric, I think pediatric is an interesting area of research as well as quite challenging, because obviously,

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pediatrics are not that much involved in clinical studies so we do not have sufficient knowledge of physiology. And there are sometimes scarce and contradictory data.

So one of them is basically gastric emptying. So there is some publication which says that the gastric emptying is related to the age. Some people say that it is not. So in such case, what to do? What is the physiology that you should use?

So probably in such cases there is a solution that you need to look and understand and collect all the information available, and then perform a scientific meta-analysis to see whether you can find some sort of relationship or not.

We tried to do it, and it is published now, the paper in DMD, that there is no age relationship of gastric emptying. However, there is a strong relationship with the food, and the food taken by pediatric at various ages is different. So basically the food, because of the type of food they eat at different ages, probably that is why

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they are seeing different gastric emptying time, not necessarily because of the age.

Again, when you have unknown or uncertain parameter, what should be the qualification criteria? When can you accept the model?

This is a third application predicting the food effect. So I think there are a number of examples here, but the main question is, sometimes you have some parameters which are not experimentally measured, and people tend to use QSAR model to estimate those parameter. Or basically you can estimate something from chemical structure -- for example, permeability or PK -- and use it to make a prediction.

I came across quite interesting example recently, and they used QSAR. But when used experimental data, their conclusion was totally different. So you need to make sure, when you have some parameters, whether they are acceptable. If not, then are you going to recommend them to go and measure experimentally? Or what is the minimum number of parameters that can be estimated?

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Another application is IVIVC. So I think with PBPK there was a lot of discussion, and this is one of the potential area that can have more confidence. So we tried to compare PBPK with conventional approach and I think I don't have lot of time to go in detail. But the same approach was taken up by a colleague in FDA, Bipin and Marilyn. So they basically tried to assess the application of mechanistic IVIVC at population level. They had access to individual data.

They perform two type of validation. Leave one formulation out, which is typical. So every time, they left one formulation out and tried to see how well the IVIVC predict for an unknown formulation. And they also performed a bootstrap.

But I think, on top of that, they performed an interesting analysis because the purpose of IVIVC is to predict for an unknown person or unknown population. So they left one individual out to see whether the IVIVC can predict all three formulations for a missed-out subject.

This is another application where they tried

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to assess the equivalence at PD level rather than PK. So you can see that for ibuprofen, the PK level, there is a strong discrimination. But because of the flat response profile, there is not much discrimination.

This is a final and very important example I wanted to discuss. So again, we generally assume that the bioequivalence at healthy subjects is valid for a patient population. But when you look at it for ketoconazole and posaconazole, because of the behavior of the drug and formulation, if the drug was bioequivalent in fasted condition, does not necessarily mean that they are equivalent in fed condition.

There are certain conditions which are more discriminatory than another condition. So probably this type of simulation can also help what should be the bioequivalent study design which can allow you to discriminate to the best possible way for different formulation.

So to summarize, we need to have more case examples to improve the confidence in PBPK. The

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second and most important is that we need to have more than qualification criteria. What is acceptable model. Then we need to establish good practices to improve the application of PBPK in regulating modeling because at the moment, if you look, there are multiple types of models available and people use PBPK with a lot of different things. So you need to have some sort of an idea of what is good practice.

We need to understand more about interoccasion variability. I think there was a discussion, and FDA is already funding some grants to do and understand more about how the human physiology changes on different occasion, and how the formulation will behave.

I think we need to also have some more research on modified and enabling formulation, as well as assessing the mechanistic assessment of excipient impact; for example, cyclodextrin exchange as well as some of the enabling formulation where polymer is used to inhibit precipitation, et cetera. And thank you.

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DR. LIONBERGER: Thank you.
DR. UHL: So I'll ask my same question I've asked many times. Your previous slide had at least half a dozen or more suggestions. If you can answer this now, what would be your number one priority, or how would you recommend prioritizing that and submit it to the docket?
DR. PATEL: Well, if given a choice, I would invest all $20 million in this so we sort it out.
(Laughter.)
DR. UHL: Well, that's true. But you have a lot of suggestions related to PBPK.
DR. PATEL: Yes.
DR. UHL: So that, in the context of generic drug development, which do you think would be most impactful?
DR. PATEL: I think, with the current status and based on some discussions yesterday, I would say we need to first arrive at what is a qualified model and what are the good practices. So once we set up our baseline where the model works and where it doesn't, with current knowledge, then we can

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move further.
So I think for a first priority, I think we need to set up some sort of a model qualification criteria and what is acceptable model, what are the good practices, and then see how well the prediction performs.
So basically, there needs to be some assessment of case examples where you can assess in what cases you have good confidence or less. So there needs to be more research on generating case examples and generating some good practice guidelines, and then the rest of them can be followed up.
DR. LIONBERGER: Thank you very much. Oh, I'm sorry.
MS. PEREZ: You mentioned that we need more research and then sort it that way. But when you say we need more research, are you suggesting the FDA does more research on this, or the industry, or yourself? Who is going to conduct this research and come up with these parameters for the industry?
DR. PATEL: Yes. I think, yes, that's a

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very good question. So I think if you look at the points, there are certain points where I think we need more regulatory input. For example, what is good practice? What is good model qualification criteria? Where we need more input from regulators and based on your own understanding or assessment? Certain of research items, like interoccasion, it can be funded by government or it can be funded by academia or industry, et cetera.
So there are certain aspects which can be done independent of regulatory funding, but there are certain aspects where we need at least some sort of cooperation between industry, academia, and regulators to come up to a conclusion that -- and this is not an easy question to answer. What is qualified model is ongoing debate and discussion. So it requires, really, a strong effort.
I think I forgot to mention about the OrBiTo project, which is an interdisciplinary project where a lot of effort has gone in to see where the models can predict and where it cannot, what should be the qualification criteria, and what should be

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the good practices, et cetera. So I think there is a need to have an interdisciplinary research approach to arrive at some conclusion on what is the good practice.
MS. PEREZ: Thank you.
DR. PATEL: Okay. Thank you.
DR. LIONBERGER: Thank you very much.
So our next speaker is Russ Rackley from Mylan.
Presentation – Russ Rackley
MR. RACKLEY: Okay. Thank you. I'm Russ Rackley. I'm head of global PKDM at Mylan Incorporated. And I want to thank you all for letting me make a brief presentation today. These are my views and not necessarily those of the official opinions or policy of Mylan.
But I will speak to the challenges with the demonstration of statistical noninferiority of adhesion and irritation for transdermal drug delivery systems using the OGD bioguidance method.
So I'll get right to the issue here. The problem with the current adhesion or irritation

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noninferiority testing is based on using OGD's recommended scoring scale. When a product scores very well or performs well, the adhesion or irritation scores are zero or approach zero.

So for the current guidance, the noninferiority margin is proportional to the mean score of the RLD. And the consequence of that is its noninferiority margin also then approaches zero.

So one thing, one comment: In my experience of 15 years at Mylan, and seeing a lot of evolution over time, I think this may not initially have been as much of a problem. But we're seeing more RLDs that are performing very well, and this is where the challenge comes in.

So the requirement is forcing generics practically to perform as a superior product relative to the RLD and/or could potentially require extraordinary powering considerations. And that's in a space, as I'll illustrate, where there's little room to improve already on what we consider good product. So Mylan believes the

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current guidance, although again not intended to do so, effectively serves as an inappropriate block to generic approvals.

So I'll briefly touch on the criteria here, the statistical test, as outlined in the current guidances. And this is for adhesion and/or irritation. Basically, we're looking at a one-sided test for the 95 percent upper confidence interval based on the mean test score minus 1.25 times the mean reference score. And this should be less than or equal to zero.

The point I just want to make on this equation is it could be rearranged so that you could show the mean reference score in the denominator. So as you have a mean reference score that approaches zero, as we're starting to see more and more of, this greatly inflates the metric such that it becomes very stringent to meet the criteria against any kind of constant or criteria for noninferiority.

I'll try to illustrate that a little bit with this graph. I've illustrated here a graph of

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test mean irritation on the Y-axis and reference irritation on the X-axis. And there's a line of identity there you'll see that goes where the test and reference would be equal. The dashed red line shows where the criteria for noninferiority would be, and it's proportional based on the ratio of 1.25.

So as you approach to zero, this margin effectively diminishes. So test products are forced into a performance at very low levels, so around a mean score reference of 1. There's a little space there to operate or perform relative to the same level as the reference product.

But as the reference scores become lower and lower, this forces the performance of the test product -- the generic, that is -- to be lower and lower again and squeezed into an area where there's little room for improvement. And the performance is superior in that there has to have almost a lower score, or does have to have a lower score.

I'm going to illustrate this with two examples based on some actual data. This is

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example one, illustrating good adhesion performance. On the left panel is data for the generic, and on the right is the reference listed drug. And this is based on 36 subjects that wore a high-strength patch for one 24-hour interval.

Adhesion was checked at 4-hour intervals per the OGD adhesion scale. And the scale score is again zero -- it was the best performance -- 1, 2 and 3. One is 90, or zero is greater than 90 percent, greater than or equal to 90 percent. One is 90 to 75. Two is 75 to 50. Three is less than 50 percent adhesion.

Over at the first check, at 4 hours, there's very good performance. Nearly all subjects have a score of zero. There's good adhesion. As time goes on, there's a little bit of disadhesion over time, and you'll see some distributions go out to scores of 1, 2, and 3, and so forth.

If you sum these scores over time, you'll get the cumulative adhesion scores for each product. And that's illustrated here graphically in this bar chart, with the blue bars representing

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the test product, the generic. And it looks like the lighter bars up there -- maybe I'm colorblind. On here it's blue, but up there it's grey. It's switched. But anyway, the left side is the test. The right side for each pair is the reference.

The point here is that there's a very good -- there's a high proportion of zero scores in this dataset. Distributions are fairly comparable as you go out and tail out. So overall, this represents very good-performing products.

So in fact, the total observations for the test product was such that 86 percent of observations had a score of zero, again accounting for all observations. The reference had 85 percent of all scores equal to zero.

We look at the mean adhesions on these, and they're identical at 0.181. And we look at the metric here, and the upper confidence interval is 0.0225, which is greater than zero, so it fails the metric in this case.

If you consider this amount, this interval above zero, it effectively relates to -- the test

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would have had to perform about 12 percent or more better to shift everything down and meet the criteria. So that's what I'm getting to, is in terms of -- there seems to be push to a superior performance aspect.

Moving on, and these are busy slides, but this is a similar kind of situation where we're getting moderate scores, in this case irritation. It could apply to adhesion as well. This was a study in which 36 subjects wore a patch daily over 21 days with same site application. Again, the left side is the generic. The right side is a reference.

Starting out, both products have roughly -- about a third of the subjects had scores of zero. So even after one application, there's very few subjects that --there's a minority of subjects that had no irritation, and more that had barely observable irritation. And that distribution shifts over time as the study's conducted to 21 days.

Again, if we sum the scores over 21 days per

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each of the observed irritation scales, scores in this case, you get the bottom score, which is a cumulative irritation value. And that's illustrated again the distribution in this chart.

So you'll see the preponderance of scores. Again, on the left is the generic. The right is the reference. Predominately scores of 1, which again is barely perceptible erythema on the dermal scale; or a 2, which is definite erythema, or could be a combination of scores of dermal and other scores. But the point is, there is a very similar pattern and distribution, again predominant around 1 and 2 for most subjects across the study.

If we look at the summary on this, you'll see similar mean scores of about 2. The upper confidence interval is minus .41, which is well below the criteria, so it would pass. There's enough space there in that interval such that you could almost be 15 to 20 percent higher relative to the reference and it would probably pass. And that's normal for a bioequivalence type of consideration, but this is one-sided with respect

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to noninferiority.

The current OGD guidance method suffers from the use of nonlinear discrete scale, good adhesion or irritation results, and datasets consisting largely of zeros. And as a result, as the reference approaches zero, the margin essentially disappears, which again forces the generic to essentially perform in a superior manner and/or could require extraordinarily high numbers of subjects from a powering point of view.

Thus, there's a need for an updated noninferiority testing method for both adhesion and irritation that will span the spectrum of RLD performance, particularly for well-performing RLDs, which predominately score out at zero, according to the scales.

We've contemplated some alternatives. One would be just change the scale for adhesion so it directly relates to performance of the product. So you could use any kind of score, but as long as it relates to in this case it could be a 9 or 95 down to a lower score, but relates proportionately to

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the degree of adhesion observed in the clinic during the study. And I just note this because the EMEA has endorsed this approach, and we feel this method should be considered in reevaluation.

A more simplistic approach might be simply to adjust the scale. Rather than start it at zero, start it at 1. This is effectively adding 1 to your overall scoring. So this would compensate for the problems that we have with the metric, and it would be a very simple solution to implement, and would accommodate the issue for both irritation and adhesion.

So questions? Does OGD agree with the current metrics for noninferiority testing for adhesion and irritation that need to be modified to accommodate all types of product responses? And can OGD promptly provide an alternative method for generic companies to fairly compare their products to the RLDs across the full range or spectrum of RLD responses anticipated for both adhesion and irritation?

Again, acknowledge this has been an ongoing

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consideration, but we are seeking some consideration. And I have already pre-prioritized this as an issue for recommendation. So I'll take some questions.

DR. UHL: Yes. So can you tell me what your priorities are, then? Because you actually asked us questions, which is not the forum in a Part 15 hearing. The agency gets to ask the questions. So if you want to prioritize, that would be great. And I have a follow-up question for you as well.

MR. RACKLEY: Okay. Really, it's coming back to I prioritized these questions for the panel to consider. So really, the issue is fundamental. It's around the scales that the OGD, I think, use. It relates to use of zero for identifying with good performance, which is somewhat counterintuitive, I think. But it depends on which way you look at the scales.

So it's almost as though any other score other than zero might work in this situation. There are other ways to go about it using different perhaps statistical approaches or other

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considerations. But I see the root of the issue as being how to address the scale itself.

DR. UHL: Okay. So I appreciate that. I just want some clarity on your concern here because on your second slide, you say that this is for good-performing products. So I just want to understand what good-performing products means. Is that products that have good adhesion?

MR. RACKLEY: Yes.

DR. UHL: Okay. So for --

MR. RACKLEY: And/or low irritation.

DR. UHL: Okay, so for product --

MR. RACKLEY: So clinically speaking, you want a patch that has great adhesion, performs well, and it consequently will score as a zero. It should have low irritation as well, ideally, and will consequently also score as a zero.

So the problem exists the way the guidances are written for both adhesion and irritation in that scores of zero reflect good performance of the product, of the RLD, is what drives the criteria here.

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DR. UHL: I appreciate that. So what you're saying is that this aspect of the noninferiority testing problems that you're pointing out are relevant for patches that are highly adherent?

MR. RACKLEY: Yes, highly adhering, low irritating.

DR. UHL: Right.

MR. RACKLEY: This occurs, as I mentioned -- we see this more and more, I think, for some RLDs. They may have one or both of these parameters that perform that way. So it presents a problem, that the probability of encountering this is fairly high.

That's where we see the issue, how to address this when RLDs -- when you have to go up against an RLD that forces you to want to perform better, but there's little room to improve on a product that's already getting the best possible score sometimes.

DR. CONNER: Yes. Since this a regulatory research meeting, in this particular topic, what are your research ideas? Where would you like us

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to focus research dollars on addressing this, or related issues to this? Do you have any kind of projects or things that need -- questions that you feel need to be answered through research?

MR. RACKLEY: There's a wealth of data out there already that have been, I'm sure, submitted. And I believe this is a problem that is throughout the industry. So datasets are there that could be taken and potentially used in evaluations via simulations, bootstrapping considerations, that sort of thing, to really explore how best to -- if one were to modify either the scale or the metric, how to modify that sort of data.

So the question would be, then, how would you disseminate or make that data available? It needs to be relevant data relative to actual kinds of observations that are seen in these kinds of studies.

DR. CONNER: Also, I think, one of your first slides you specified the current noninferiority method that we're using. But I think that we've gone beyond this. This is not

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entirely 100 percent accurate since we've added a 90 percent role on top of that, which I think we have actually discussed with some of your -- some of the GPhA member companies who had issue with this.

So this isn't the complete story on how we handle these, although, granted it is still an issue, and it's still worthy of pursuing. But it's not entirely 100 percent accurate, as far as that goes.

MR. RACKLEY: Well, I don't know that it -- yes, I didn't know if that was necessarily public knowledge, so I did not really comment on that. But I don't know that it necessarily, as I'm referring to this, really deals with the full spectrum of RLD responses, so from 100 percent down -- or from scores of zero to whatever the maximum score is.

So you can think of this as percentage of adhesion if you want to, so from 100 percent adhesion down to zero percent adhesion. So I don't know that it fully covers. I mean it covers one

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end. It's not a problem on the other end. There's still a potential problem in the middle.

DR. LIONBERGER: Thank you.

So our next speaker is David Schoneker, representing IPEC Americas.

Presentation – David Schoneker

MR. SCHONEKER: I'd like to thank the FDA for giving me the opportunity to speak on a topic near and dear to us at IPEC Americas today. We've heard a lot throughout the day, almost from every speaker, about the importance of excipients in a lot of different ways -- the importance to formulation science, manufacturing science, pediatrics. Ajaz brought up the need for simple versus complex formulations.

I'd like to put that into perspective with what's really happening out there that I'd like to talk about. And that is, we talk about the need for more focus and more science in the area of the impact of excipients on formulation quality and performance, which is what's really key.

But before formulators start picking

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excipients for formulations based on that kind of data, the first thing they have to address is the safety of the excipient. So that's actually the first and the biggest driver that's actually going into drug development today.

Unfortunately, due to the inappropriate use of some of the existing tools, and the lack of some new tools that are needed, we're finding that this is driving generic drug development, in some cases, in the wrong direction.

Now, I'd like to coin a new term today. We've heard a lot about QbD, QbR. I'd like to talk about QbI. And QbI is quality by IID. Okay? Because that, as I go around the country and around the world talking to generic companies, is what's driving how many generic drug formulations are in fact developed. And I'll talk more about that as I go through the slides.

So IPEC Americas, as with GPhA, we have a lot of members. We have over 80 member companies here in the US, over 350 member companies around the world, and we represent many of the biggest

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generic OTC innovator drug companies, most of the major excipient companies all over the world.

So some of our key concerns, getting at my points earlier, is that we believe that some of the current OGD policies and guidance for generic drugs related to excipient safety review are really not science- and risk-based.

We like to talk a lot about science- and risk-based, but what we see actually happening is not necessarily so, based on good toxicology and good safety reviews used throughout the world. It's not really aligned sometimes even with the way these materials get looked at by other areas, even within the FDA, from the new drug side, to CFSAN, to the cosmetic folks.

The current policies and guidances, such as the RTR guidance and the controlled correspondence guidance, related to where it talks about the use of the IID are actually creating barriers to innovation and significant confusion throughout the industry.

For example, in the RTR guidance, it says

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specifically that any use of novel excipients means that it shouldn't be a generic drug, it should be a 505(b)(2). Okay? Now, I'm going to come back to the fact that novel excipients can be defined a lot of different ways, not just new chemical entity type of excipients. But I'll come back to that.

Now, IPEC Americas and GPhA has had a working group, and we've been working very closely with folks at FDA, a combination of people from many different departments in OGD and many other groups. And we've been working since 2011 to not only make improvements in the IID, but also to try to address some of the policies around how this gets used in the area of drug development.

Unfortunately, we've submitted a lot of information, had a lot of discussions, but some of the most key decisions I'll touch on today have really still not been made that are needed to be implemented by FDA, even here in 2016. So we feel that there is a need on the one hand for better coordination of some of these concepts between OPS and OGD and the industry.

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Now, putting it in context of the questions that were asked for this particular session, I'm going to focus on number 1, 5 and 6. So in the area of technical advancements that are needed to overcome specific barriers, again we believe that the current excipient safety review and the IID-related policies are stifling innovation.

It's wasting FDA resources, and resulting in the development of non-optimized generic drug product formulations. Now, I'll come back to that in a minute because that's a very interesting point.

But on number 5, what I'll be talking about is the need for a read-across approach to excipient toxicology review that is needed for the evaluation of excipient families. We tend to call that the family approach within IPEC. And that's needed in order to facilitate streamlined assessments based on good science.

This practice is the most common practice used by regulators around the world, and it's already used, as I mentioned earlier, in many other

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parts of the FDA to essentially bracket families of things like polymers where all the toxicology is the same. That's not necessarily how it gets applied in generic drug development.

The last one related to strategies for enhancing equivalent risk management. We believe that the acceptance of this family approach, and the need for an independent novel excipient qualification process, could speed up generic drug development, improve drug quality and performance, and enhance the use of advanced manufacturing techniques, such as continuous manufacturing.

Now, the ANDA process, the impact that the IID has on this -- we believe, again, some changes are needed to improve the efficiency of the ANDA process for excipient safety review. This would help the agency and industry meet GDUFA goals, apply science-based risk assessment principles, minimize reviews of redundant excipient toxicology information, and reduce confusion regarding the IID.

Now, the current IID and the associated

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policies, as it's being applied today, we believe is insufficient to support efficient drug development and approval, and we must streamline this process and use good science to assess what is the real risk.

The real risk, in most cases, many commonly used excipients are extremely safe. There's really not much of a safety issue when you're using existing materials, even at higher levels, et cetera, as I'll talk about.

So some of the new uses of existing excipients that come up in drug development, and novel excipients -- and I'll say that are not new chemical entities because FDA's own definition of a novel excipient includes new chemical entities, coprocessed excipients, higher levels of existing excipients, new routes of administration, coprocessed excipients, et cetera.

If we can use these materials more effectively, and again, recognizing that new chemical entity type of excipients might be more appropriate for innovator drugs, but a lot of these

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other types of novel excipients are being avoided in many different ways.

If we can use these, it would enhance high quality generic drug development at equivalent performance to innovator drugs in many cases. It would also allow us to improve manufacturing productivity and help control the cost of the generic drugs.

Now, this next point I want to elaborate on just a bit. I said many generics are being designed with less than optimum formulations due to barriers in the excipient safety review process for ANDAs.

I get out to many, many generic companies all around the world. I just came back from a week in India. I talked to hundreds and hundreds of formulators, and I've talked to many here in the US.

The thing I hear consistently from the majority of these people is that their companies have a policy in place that says under no circumstances should a formulator use any excipient

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at a level higher than what's in the IID, and since they don't know what the MDI is, that their MDI shouldn't exceed what's in the IID, which doesn't make a lot of sense.

But that's what's actually happening, and people have told me they have formulated non-optimized products just because they want to stay under the IID, even though they know they could use more of a particular excipient and get much better performance. Instead, they use, many times, multiple grades of the same excipient so they can stay under the grade level that's listed, which adds complexity and unknowns to the situation.

So the process should be consistent, we believe, with risk management concepts, good science and global toxicology practices, and quality by design principles. Some of the key things that we're looking for is, we'd like to have a standardized approach for supplying inactive ingredient information to streamline the submission and review process. We've already worked on some

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of this. We'd like to see it implemented.

We'd like to use this -- again, the excipient family approach -- to facilitate common pharm/tox evaluations for related excipients; prioritize a one-time review of excipient families where in fact the same exact toxicology will always apply to everything in that family, regardless of the context of use; and revise FDA guidance documents by correcting contradictory and inconsistent information.

So what's an excipient family? Well, again, I alluded to this before. It's many times many of the families that are the most common excipients out there, such as polymers like hypromellose, et cetera, are chemically similar but may have various grades in the family that are all covered by the same toxicological standpoint.

Hypromellose is a great example. JECFA, and in fact CFSAN, has already agreed that there is no safety difference between any grade of hypromellose. In the food arena, you can eat up to 20 grams. FDA's approved 20 grams. JECFA of WHO,

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the Joint Expert Committee on Food Additives, said there's no reason to even put a limit on hypromellose, so their ADI is not specified.

Yet in the IID, we have many grades of hypromellose, with levels as low as 40 milligrams, and people being asked for full toxicology studies on that particular grade of hypromellose to justify 100 grams, or 100 milligrams. It doesn't make any sense.

So I'll try to finish up because I know I'm about out of time here. Benefits of the family approach. Transparency to drug formulators on maximum excipient use levels by route, as supported by tox data.

This would minimize need for multiple FDA reviews of the same toxicology data once a maximum use level has been accepted. It could expedite FDA review of ANDAs, minimize errors and resources to maintain the IID, and reduce the complexity of the IID.

So our ask, if you will -- and I only have a couple, so it should be easy to see the priority

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here -- we really believe that there needs to be a formalized acceptance of a lot of the things we've already presented to the FDA related to this family approach. We pretty much presented all the science that exists to justify this.

If needed, we feel that through the regulatory sciences initiative, if there's some science that people feel is needed to be able to make this decision, we would like to see whatever studies it is that are needed to make this decision done under this initiative so that we could move this forward.

We'd also like to see revision of the RTR and controlled correspondence guidance to facilitate innovation related to the use of novel excipients that are not based on a new chemical entity, and work with industry to investigate the development of an independent novel excipient qualification process outside of the drug approval process. This could save everybody a lot of time.

Finally, I'd agree with GPhA, there's a need to set up industry working groups to look at the

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priorities and investigate specific projects beyond what we've done in the past. So with that, I'd like to stop and ask for any questions.

DR. LIONBERGER: Thank you.

MR. SCHONEKER: Thank you.

DR. UHL: So based on your comments specific to the RTR and the controlled correspondence guidance, did IPEC send comments to the docket when those were published?

MR. SCHONEKER: Multiple times. We brought it up in every one of our meetings. We've sent comments in. We've been talking about it since 2011 in every venue we can. But we haven't been able to get a decision on some of these things, and that's what we're not understanding.

If there is some science that's needed to be able to get the decisions made internally that are necessary, let us know what it is, and maybe we can work through this venue or through any other venue to get that science there that's needed, if there's anything.

We're not sure what is needed because this

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approach we talk about here is what's used by every regulatory agency in the world, and we've brought in world-class experts to testify to that already.

DR. UHL: Thank you. I have a follow-on question unrelated to that. Your third bullet is an independent novel excipient qualification process. So could you elaborate a bit on what that would look like?

MR. SCHONEKER: I could. And in fact, we've already started some initial discussions on that. We did meet with Susan Zuk. We've put a meeting together with some of the FDA toxicologists, both from OGD and the new drug side, back last year to initiate a discussion on how could we set something like this up.

What came out of that discussion was, this is something that -- it's different, but it could look something like what goes on with the biomarker qualification process, where you could have something where there's an intended use established, an intended exposure level established, and then the safety data could be

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presented to an appropriate group that could then make a recommendation not to approve the material but to qualify the material for those applications up to a specific use level, whatever, based on the actual safety data that exists for the excipient.

It is a situation that could be funded through user fees or through other mechanisms. We proposed a lot of those things. And what came back was there was an interest. I know I've talked to Lawrence Yu about this as well, and what we're doing in industry is both IPEC and the IQ Consortium is having some discussion. And we've been having discussions with GPhA as well, about how we could actually now take that concept that we talked about and make a proposal to FDA for you to review about how we could set something like that up that would be an independent review process.

Because part of the problem we have here is until we can have the excipient safety not become an issue, that ends up dominating the formulation discussions way beyond what the actual technical issues are, where we should be spending the

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resources about how to make better formulations, how to improve quality by design, prepare things, or even develop excipients that would enhance things like continuous manufacturing.

But without addressing some mechanism to get beyond this sort of safety concern that the generic industry has, then nobody touches that. I guess you could say it's QbF, quality by fear in that situation. So somehow we've got to resolve that because otherwise we're just going to keep fighting that all the time.

DR. UHL: Good.

MR. SCHONEKER: Thank you.

DR. BOAM: Hi, David. Thanks for the presentation. With respect to the family approach, I was going to ask whether you or your organization had a chance to follow up on thoughts about using the critical path innovation meeting approach to try to have discussions about that? And if you've gotten some feedback on that, what feedback you might have gotten.

MR. SCHONEKER: Well, and I know -- yes.

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Well, Susan had told us that that might be an avenue to pursue, and we're actually having internal discussions now, both within IPEC, the IQ, and GPhA as well, is how can we come into that process. Again, it's not a process we're that familiar with yet, but we want to get familiar and then try to utilize that process in the near future to make these proposals I was talking about.

Because we think that's a great idea. And again, we think that could tie into some of the science objectives too, because if there's some studies needed, some science that's needed, some need to address guidelines, all of this could be focused in there. Thank you.

DR. LIONBERGER: All right. Thank you very much.

MR. SCHONEKER: Okay, thanks.

DR. LIONBERGER: We will now take a 15-minute break, and we'll reconvene at 3:20.

(Whereupon, at 3:05 p.m., a recess was taken.)

DR. LIONBERGER: Welcome back, everyone.

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Please take your seats so we can begin the final session of this meeting.

Our next speaker is Bahman Asgharian from Applied Research Associates. Welcome.

Presentation – Bahman Asgharian

DR. ASGHARIAN: Thank you for the opportunity to be here. I would like to present a research idea that has been made possible by recent advances in our computing resources and image technologies.

I will be talking about the reconstruction of lung airway trees to detect earliest stages of disease in the children with lung disease, and following it up by computation of three dynamic calculations to study lung ventilation and drug delivery. This type of work actually complements PD/PK modeling in the sense of reducing uncertainty for the dose that goes as input to the PK or PDPK models.

So the motivation for the proposed idea is to explore novel airway modeling techniques to detect lung disease at earliest stages before the

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disease has a chance to damage or destroy lung airways, and look for that, the window of opportunity for drug intervention and treatment.

Also, use the modeling technique to explore new ways to target drug to the affected sites where we know, because of the damage, the lung is resistant to airflow and drug getting there. And at the same time, reduce the drug delivery to the sites that it typically goes to, undesired sites, and as a result, minimize the side effects.

3D modeling of the lung children, it cause high-resolution imaging. And this imaging actually is available already from other studies for both the diseased lungs and for healthy lungs of children.

The idea I am proposing would add these knowledge gaps that have been identified by the FDA in terms of physiological variability within a subject, leveraging complex models and computing, model validation when we don't have data, and understanding the physiology in subpopulation -- in this particular case would be children with lung

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disease.

The example I will be presenting is cystic fibrosis. Cystic fibrosis is a chronic disease which targets the lungs mainly and start with the upper lobes of the lung. So the disease actually -- the changes to the lung due to the disease starts early in life.

The way it's being diagnosed is they take CTs of the lungs, and those CT images we can use for the ideas I am proposing. So the treatment for this disease is to try to reduce the severity of the symptoms and slow the progression. However, intervention is the key. You have to intervene early, before the lung airways are damaged.

So the problem is that detecting this disease at the earliest is a challenge. We have to look for biomarkers, variables, that can allow us to do that. The objective would be explore novel airway modeling techniques, and that includes 3D lung airway reconstruction and conducting computation of fluid dynamic studies in this geometry. And by doing the 3D reconstruction, we

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look for variables that are associated with the disease.

This could include the bronchial cross-sectional area, airway partitioning between healthy and diseased lobes, airway resistant, impedance, and other parameters.

By doing the computational fluid dynamic studies, we would like to study drug delivery to the -- first we would like to study the airflow distribution, from which we can calculate or we can estimate the lung function that we need to use as the biomarker. And then next would be to study drug delivery to the diseased lung.

This step actually is pretty extensive and needs an expert of people in the field to do it. However, it would be desirable to have this package in a simpler way, like a multiple-path dosimetry model that allows clinicians and other health professionals to run the model for the specific patient on desktop computers.

This model I'm talking about is a 1D representation of the whole 3D modeling. It's been

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simplified so it can run fast with fairly good accuracy, and has already been developed for healthy lungs. And the next step would be to include the diseased lung at different stages into this model.

Some preliminary results have already been obtained. First, there are 8 CT scan of the lungs of the kids, children with CF, 4 males, 4 females, and ages from 3 months to 5 years old. And this data has been collected as part of an NIH study with PI Stephanie Davis and co-PI Julia Kimbell.

These are the reconstruction of all these airways from -- it's a 3 month old girl, 10 months, 12 months and 3-year-old girls, one 3-year-old boy and three 5-year-old boys. So we did some preliminary studies on these reconstructions.

The first thing we did was we calculated the cross-sectional area of the left and right main bronchi from reconstruction of the airway tree that went down at least three generations, and then we expressed it as a percentage of the total cross-sectional area.

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The same we did for the lung ventilation, calculated it by doing CFD studies assuming steady-state respiratory flow at resting breathing rate. We calculated the lung airflow going to the left and right lobe. And then also we expressed that as the fraction of the total inhaled airflow.

This is the results. I'm just showing the sense of it. On the left panel, we have plotted for each subject the airflow rate and the cross-sectional area in blue and red bars. And on the right, you have these two parameters plotted against each other. So early findings is that it show that actual the airflow distribution between left and right lobes are generally similar to the cross-sectional area between the two main bronchis.

There is also some work ongoing which I'll touch on that, looking at two 12-month-old CF subjects. So further work is needed to validate the accuracy of these reconstructions, and also look for other variables that might be of interest to detect the disease.

So these two actually would be very useful,

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have the potential to quantify the effect of CF at early age on lung structure and lung function. Based on that, we can develop treatment policies. These are the two 12-month-old subjects I just mentioned, so subject-1 top, subject-2 bottom. Left column shows you reconstruction of the lung at the end of inhalation. The right column shows at the end of exhalation. And there's a big difference.

You can see the lung has shrunk at the end of exhalation. So this is actually to see -- the reason we see that, on the left the airways are fully expanded on the inhalation, but they disappear at the end of exhalation. And this is because airways have collapsed.

There are additional data available, so these were just two. There were over 50 scans, CT scans, of the lungs of 12-month-old children, and in addition, images are available for healthy kids from birth to 17 years old from a different R01 study. So this database can basically be the foundation to study drug delivery to diseased lung

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and the dosing in healthy and diseased lung.

The last slide, I have personally noticed recent interest by the FDA on doing CFD studies. And what I'm trying to promote is that we probably should be -- if data is available, should be using actual scans rather than using idealized geometry, which I have seen that a lot recently. And this data are already available.

For this particular case, recommendation is to use the 3D reconstruction of the CT scans of the children with disease, and compare that with the lung reconstruction of children with healthy lungs for which scans are available, then, to study these biomarkers. And conduct computational fluid dynamic studies to study airflow in the lungs of both healthy and diseased lungs.

Then look for possible ways to maximize airflow and drug delivery to the lobes that are affected. As I mentioned, they're hard to get to normally because the lungs are damaged. And also minimize the side effects as the results of drug going to these sites that are not of interest.

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Then we would like, as I mentioned earlier, that we would like to package this is in a multiple-path dosimetry model to allow clinicians and health professionals to be able to run this for a specific patient on desktop computers. And finally, be able to validate these models by comparing with experimental measurements. Thank you.

DR. LIONBERGER: So can you say what would the impact of this be on the development of generic drug products?

DR. ASGHARIAN: Well, this actually is the framework for any drugs, so if that could be -- so basically, this is a generic model that can be applied to any scenario, including generic drugs. So that's the whole idea, that it's not anything specific.

DR. LIONBERGER: All right. Thanks very much.

DR. ASGHARIAN: Sure.

DR. LIONBERGER: So move on to our next speaker. It will be Tracy Rupp from the National

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Center for Health Research.

Presentation – Tracy Rupp

DR. RUPP: Good afternoon. Thank you for the opportunity to speak today. My name is Tracy Rupp. I am a pharmacist and the director of Public Health Policy Initiatives at the National Center for Health Research.

Our research center analyzes medical and scientific data and provides objective health information to patients, providers, and policymakers. We don't accept funding from the drug or medical device industry, and I have no other conflicts of interest.

The first policy issue or GDUFA research issue that I'd like to talk about is the inspection of manufacturing plants. We've heard today that patient and prescriber confidence in generics is disproportionately shaped by the recalls and quality issues that occur.

So increased attention to manufacturing and quality control is critical. And importantly, we have heard how bioequivalency for complex generic

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drugs is highly dependent on the quality control of the manufacturing process.

In 2012 Congress passed the FDA Safety and Innovation Act, or FDASIA, which among other things requires the agency to inspect foreign facilities that make drugs sold in the United States as frequently as it inspects domestic plants.

In addition to achieving parity in the frequency of inspections, FDA also committed to ensuring that domestic and foreign inspections are conducted with comparable depth and rigor.

A 2015 report from the Office of the Inspector General found that FDA has made progress on oversight and inspection of manufacturers of generic drugs, but gaps remain.

For example, FDA increased its preapproval inspections by 60 percent between 2011 and 2013. However, it didn't conduct all of the preapproval inspections requested by its own generic drug application reviewers during this time period. And most unfulfilled requests were for inspections of foreign manufacturers.

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FDA staff attributed the outstanding preapproval inspections to a lack of resources. And in addition to improving drug quality and improving consumer confidence in generics, timely conduct of preapproval inspections could help reduce delays in the availability of generic drugs.

In recent years, FDA has sent warning letters about violations to companies with plants in foreign countries, such as India and China. The number of warning letters sent to Chinese and Indian manufacturers for violations nearly quadrupled from 2012 to 2015. Most of the warning letters raised concerns about data integrity.

Many of the observations were for egregious problems, like altering official documents in front of an inspector, falsifying dates of quality control testing, or documenting important manufacturing data on scrap paper in pencil. And these are the types of issues that can clearly impact consumer confidence in generic drugs.

Despite the increased resources from the GDUFA provisions of FDASIA in 2012, it's difficult

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to keep up with the increasing production of drugs and devices in foreign countries. Imports of drugs and medical devices from China alone increased by nearly fivefold from 2007 to 2013.

The 2015 OIG report recommended that FDA use its inspection resources more efficiently by making greater use of authority granted by FDASIA to request records in lieu of, or in advance of, an inspection. The authority could increase FDA's capacity for preapproval inspections. Record reviews could be completed in advance rather than using up the inspection staff's time during an onsite inspection. The inspector's time onsite could be prioritized to address the tasks that must be conducted in person rather than on reviewing paperwork.

Two important questions are: Has FDA implemented this recommendation? And if so, what impact has it had? Additional related regulatory science research questions could include: Has this new authority improved the quality of inspections? Has it helped FDA hone in on the issues posing the

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greatest risk to public health?
Can a more focused onsite review help improve drug quality and reduce the risk of patient harm from unsafe drugs? Does this new authority reduce approval delays? Do more frequent preapproval inspections result in fewer recalls? And are problems identified and fixed earlier as a result?
Another important GDUFA regulatory science research question is how to improve compliance with the requirement for manufacturers of generic drugs to register with the FDA. FDA uses the registration database to help determine which facilities to inspect, using its risk-based approach.
The OIG found that of the 432 generic drug manufacturers listed on ANDAs approved in 2013, 10 percent didn't match entries in FDA's registry of generic manufacturers. It's worth noting that 62 percent of the manufacturers that couldn't be located in the registry were foreign.
FDA can't inspect facilities if it doesn't

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know they exist. So research is needed to determine what strategies are most effective for ensuring registration, including incentives for registering and effective penalties for those that don't.
Another important regulatory science question is the effect of generic drug labeling updates on patient safety. FDA has issued a proposed rule that would allow manufacturers of generic drugs to update their label with new information as it becomes available. And we strongly support that rule.
Currently, generic manufacturers have little incentive to monitor drug safety, and they aren't required to update the label with new risk information. As a result, safety monitoring basically stops when generics enter the market.
This puts patients at risk, since the FDA found that the median time from initial approval of the drug product to the time of making a safety-related labeling change was 11 years, past the market exclusivity period for many branded

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drugs.
The proposed rule would give generic manufacturers the authority to initiate safety labeling changes through the changes being effected process. And the result will be to give patients access to the most up-to-date product labeling.
It would be helpful if the FDA could conduct or support research to determine the impact of the current situation, where labels for generic drugs are not updated unless the branded version is updated. It's especially important to compare the current situation with previous policies.
For example, prior to the Supreme Court decision Pliva v. Mensing in 2011, generic drug companies were responsible for updating their labels. Now that they're not required to update the labels, an interesting question is how many labels for generic drugs were updated in the five years prior to the Supreme Court decision compared to how many have been updated since.
When and if the proposed rule is implemented in the future, an important question is how will

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this affect the timeliness, accuracy and completeness of drug safety labeling, and will it protect patients from harm?
The third and last regulatory science question I'll mention today is related to patient copay coupons. Like we heard earlier today, as drug costs continue to rise, brand name manufacturers are more likely to use coupons to entice customers to fill their prescriptions since coupons defray or eliminate the copay costs.
In 2009, coupons were available for fewer than 100 prescription medicines, but the number exceeded 700 by last year, according to a recent analysis by the Tufts Center for the Study of Drug Development. These coupons are more common just prior to generic competitors coming on the market. The goal is to establish brand loyalty and reduce the number of patients switching to generic versions.
As we heard earlier today, a 2013 New England Journal of Medicine analysis found that 62 percent of coupons were for brand-name drugs for

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which a lower cost option existed.
The important regulatory science questions related to copay coupons include: How do coupons affect prescribing of generic drugs? What impact do coupons have on patient outcomes, such as adherence to therapy and treatment success? And what is the impact on cost for patients for Medicare and private insurers?
In summary, generic drug research and policies have an enormous impact on the health and safety of millions of Americans, and impact patient and prescriber confidence in generic drugs. We urge you to consider research that will improve drug quality through rigorous manufacturer inspections, increase patient safety through the communication of important drug information on generic drug labels, and promote the uptake of generic drugs where they have the potential to reduce cost and improve outcomes.
Thank you for the opportunity to share our recommendations today, and I'll be happy to take any questions.

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DR. LIONBERGER: Thank you.
DR. UHL: When you mentioned aspects of the inspections, and you talked about incentives for registration, do you have any other thoughts -- could you expand a bit on that? What would that look like? What are you guys thinking related to incentives?
DR. RUPP: I guess we haven't --
DR. UHL: What would be required in order to do that?
DR. RUPP: Right, right. We haven't specifically come up with any real great ideas. But we do feel like it may actually end up more in the realm of being some sort of a penalty being the incentive. But I think that there could be some further discussion between industry and the FDA and other groups, really, to what would be the best way to approach that.
DR. LIONBERGER: Well, thank you very much.
DR. RUPP: Thank you.
DR. LIONBERGER: So our next speaker is Professor James Brasseur from the University of Colorado.

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Presentation – James Brasseur
DR. BRASSEUR: Thank you very much. Just a quick background on myself since I'm rather unusual in this group. I was at Penn State University for 27 years. One of my primary areas of research was the interplay between the physiology and the mechanics of the gastrointestinal tract, particularly the fluid dynamics areas, because that's my primary area of expertise.
About 15 years ago, I began working with pharmaceutics, first with Janssen Pharmaceuticals and then with AstraZeneca. I have a long relationship with Bertil Abrahamsson and his colleagues at AstraZeneca in Sweden. And about two, three years ago, I began working with the University of Michigan, and I'm part of the FDA-funded program that Gordon Amidon and Duxin Sun discussed this morning. And this project that I'm discussing right now is in relationship to that program of research.
The focus of my discussion and my

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recommendations are the improvement in our understanding of the hydrodynamic effects on dissolution in the gastrointestinal tract, and in vitro and its effects on the absorption. and details associated with modeling such as PBPK type of approaches, and more complex types of models.
Obviously, the gastrointestinal tract functions very differently from an in vitro device. There's transport and mixing, which are both required in order to deliver any molecule to the surface, the epithelial surface. That would include nutrients as well as drug molecules. And this is a combination of different kinds of motility events that take place within the gastrointestinal tract.
It doesn't take much to notice, of course, that an in vitro device doesn't represent even approximately these, but that in itself isn't necessarily indicating that there's a lack of correspondence between the in vitro and the in vivo situation. And that's something I would like to get into.

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The primary motility events that take place in the GI tract are peristaltic or propagating wave-type contractions and segmental contractions. These are in the fed state. In the fasting state, the MMC contraction event is primarily a propagating type of event, but there are smaller, different types of contractile events, very powerful, in MMC3 and so on that are very different in that the volumes in which the dissolution process is taking place are much smaller than in the fed state. So there's very fundamental differences in the hydrodynamics associated with differences between the fed and the fasting state.

Obviously, the flow field, the velocity fields and so on, are very different than they would be in an in vitro device, and they're very different from each other in the different types of contractile events. And those are issues that we're trying to investigate and that we feel needs more work.

In particular, if one were to plot, as I'm showing here -- this is taken from rat data from

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and NSF funded program some years ago. And this is a peristaltic contractile event where the diameter is plotted as a contour plot, as a function of time. And these propagating events appear as these striped contraction reaches. Whereas in a segmental contraction, you get this checkerboard kind of a behavior which is consistent with this picture on the left.

You can imagine that the mixing process, the release of drug from particles that might be contained within these segments and so on, will be very different. And in fact, they are, and we aim to quantify that using computational fluid dynamics-type of approaches.

So here's an example of a model that we just completed developing, and we're now in the process of using, to create computational experiments in coordination with the in vivo analyses, the in vivo experimental dynamics that are being measured at University of Michigan.

All right. So what I'm showing here are 500 pharmaceutical particles being moved around in

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a simulated clean peristaltic wave. This computer is slower than it should be, so it's not moving continuously. But at any rate, these particles are releasing drugs. This is a realistic simulation for ibuprofen. The release rate is consistent with the in vivo situation. This is the fed state.

The main message to take away is that these kinds of simulations can give a lot of detail that are not available in the in vivo measurements, in the in vitro measurements, and certainly not in the standard PBPK type modeling. And in particular, you notice a lot of heterogeneity.

The uptake at the wall depends in time on this heterogeneity. The details of the heterogeneity depend on the motility and other characteristics of the gastrointestinal tract versus in vitro.

All right. The modeling has to correspond with this improved understanding. And one of the areas in which I have focused in a couple recent papers is the importance of modeling from a physics-based type modeling strategy. Models tend

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to be empirically based, and I argue that the core of models should be, as much as possible, connected to the laws of mechanics. And in particular, this representation that I'm showing here is an attempt to do that, where this object here, which has this symbol "Sh" and stands for what's called a Sherwood number, has the physics embedded in it. And this is where the true modeling part lies.

But the solubility difference with what's called the bulk concentration is another central parameter, as well as the radius. And this has come up several times in yesterday and today's meetings. But it's this parameter in which the hydrodynamics is embedded.

So one can write this expression as a first term, which is a pure diffusion model in an infinite domain, sink conditions. The second term is a correction for those sink conditions. And the third term is the hydrodynamics. And this has two effects. One is shear -- or, sorry, one is convection. This is the standard one. And one is shear, which is a new one that we've found in our

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work to be more important than convection.
So what are the mechanisms by which one can compare in vitro and in vivo? And again, it's obvious that the global flow is totally different. But that doesn't necessarily mean that the in vitro device is not relevant to the in vivo.
What matters is the release of drug from individual particles, thousands of these, that are moving through the device. And if the rate of release of drug is consistent with the in vivo scenario, then it's in vivo relevant.
The parameters that are required to describe this process of drug release are local, local to the particles of the drugs themselves. And these are fluid dynamics parameters that people in the fluid dynamics community understand. This one is called a Reynolds number. This one is called a Peclet number. But the point is that these are local to the particle.
For example, one needs to estimate the relative speed between the particle and the flow to determine these Reynolds numbers or these numbers

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that determine the rate of release of drug from the particle surface. And this is what is meant by hydrodynamic effect.
It turns out that there's another hydrodynamic effect that we discovered a couple years ago, and that's related not just to the relative speed between the particle and the flow, but to something called the shear rate. This is something in the fluid mechanics of the flow itself.
But the main point is that it's very different in this kind of a device than it is in the in vivo situation. And this is a characteristic that makes the in vivo situation different from the in vitro situation.
So these are computer simulations, for example, from the literature of a USP-2 device where this parameter that I call shear rate is up at around 100 maximum, whereas we've done simulations in our gut model, and their maximum to 2, 3, 4, 5 inverse seconds. So two orders of magnitude difference. And this is the main

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difference between the in vivo and the in vitro situation, not the global flow itself.
So these numbers, if you compare the intestines with USP 2 device, are very different, orders of magnitude different. But they're also -- this number is very different from this number, and that's another issue. So for example, if one actually does -- and so we did a large series of calculations to show this Sherwood number, which is a nondimensional release rate for the drug, as it were.
So this is the number that characterizes the hydrodynamic effect. One means no hydrodynamic effect. Numbers bigger than 1, so this is twice the non-hydrodynamic release rate, 3 times, 4 times.
What we're plotting here is against this thing that I called Peclet number. But the details aren't important. Important is that this shows that there is a large variation. depending on this number. And when you compare the in vitro with the in vivo, they're very different, so that the in

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vitro situation is releasing drug at three, four times the rate of the in vivo situation. But even in the in vivo situation, there's a broad range that has hydrodynamic effects involved in it.
So we need to understand this better. We need to include this into the modeling. It hasn't, to date, been included in the modeling. Of course, the beauty about computer simulation is you can answer the question why. Why is there enhancement? I don't have time to go into it, but in a nutshell, it's because the particles spin because of these effects, and the spinning creates a local enhancement of the release rate.
This has been validated through in vitro experiments that we did together as a group at the University of Michigan. Greg Amidon and Deanna Mudie worked with me and my team. And these were well-validated.
This is a computer simulation or mathematical model simulation compared against the data, and we validated it. It works very well. And not only does it work well, but it turns out

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it's in vivo- and in vitro-relevant. It's important. We've now validated that.

This is the last slide, which shows -- this is the standard way in which modeling is typically done in the PBPK world. And it's done used what's called a diffusion layer thickness model. And my argument is that this diffusion layer thickness model is ad hoc and it needs to be based on first principles.

In this case, we're basing it on the shear effect. And you can see that the curves, which are often represented in this form, depend on the shear rate, and the shear rate depends on the flow, the flow depends on in vitro versus in vivo, and also depends on the particle where it happens to be sitting at any given point in time.

So my take-home message is that the hydrodynamic influences are important to study. There's very little that's understood about them, and so there needs to be a lot more. But also, the modeling needs to be put on a more first principles basis, bases that are based on the conservation

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principles, what are called the laws of mechanics or the laws of physics, at the core. And I think there needs to be a movement to try to move some of these models to a more physical core.

Obviously I can only say so much in 10 minutes. There's all sorts of sub-issues that perhaps will come up in the questions right now. Thank you.

DR. LIONBERGER: All right. Thanks very much. As a chemical engineer who has taught graduate fluid mechanics, it made perfect sense to me.

(Laughter.)

DR. BRASSEUR: Excellent. Excellent.

DR. LIONBERGER: Butit's a question, right, to identify. You know the question we're looking at here is what should we, as we're preparing a regulatory science research program, look at next to advance this area?

Should we be looking at the in vitro dissolution apparatus to make them more like the physiological situation? Do we need more data on

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the in vivo physiology to confirm this? So what would be the next sort of research --

DR. BRASSEUR: Well, obviously, the emphasis of my presentation was more on the hydrodynamics and the modeling aspects. And I feel very strongly that this cannot be evolved or developed or improved in isolation of the real situation.

The real situation is that there are in vitro devices that are designed to measure dissolution for situations that are in vivo-relevant. So one of the big questions is, to what extent are they, and to what extent is that important? So these need to be integrated, and I already gave you one example of where we have done that.

But it also needs to be integrated with the in vivo scenario. And the in vivo scenario is a rather different one. You can do certain things with modeling and on the computer that you can't do in vivo and vice versa.

So the real challenge is to integrate them in a way that advances our knowledge and our

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modeling capabilities, and that's of course what we're trying to do at the University of Michigan with me and my team. And I think there needs to be more of that kind of integration done.

DR. LIONBERGER: Thanks very much. So our final speaker is Professor Jim Polli from the University of Maryland.

Presentation – Jim Polli

DR. POLLI: Okay. I apologize, I do not have any good videos. So a lot of people have already mentioned, talked about excipients, so I'll try to just be brief. My major comment is it would probably be good to do more excipient-based research.

As the group knows, drug product quality is a major focus. There's a need over the lifespan of products to make sure their quality is assured, both before generics and after generics. So there's always a need for equivalence testing.

So here we have two formulas, one of the innovator product of lamotrigine and one an example generic of lamotrigine. And it probably would be

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very interesting if we were to take a survey of various folks -- healthcare providers, pharmaceutical scientists, what have you -- when they look at this, what is it that they see? What sort of risks do they see? And I would suggest that there's huge differences in points of view among various stakeholders in how they would describe similarity or differences between these two formulations.

But arguably, a major area where differences can occur are excipients. And then we can ask the same question: Well, is there a difference between lactose and lactose monohydrate in the context of ongoing drug product quality?

To some extent that's been answered, but to a fair extent it hasn't. And I think this uncertainty has persisted for a long time, and it would be helpful from a biopharmaceutic standpoint to have better-developed literature around excipients, or at least the most common excipients.

So as everyone knows, there are biowaivers. There are all sorts of different types of

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biowaivers, including so called Biopharmaceutics Classification System-based biowaivers where the focus is on applying biowaivers using in vitro testing, et cetera, to so-called less risky drugs. But then the question is, which are those? And within the last year, the FDA put out a guidance that expanded the BCS to include so-called Class III drugs, drugs with high solubility and low permeability.

This is from an article from the FDA from a couple years ago illustrating the distribution in ANDAs with regard to BCS Class I, II, III and IV. And Class I and III make up a large part of drugs that are in ANDA applications. So it seems as if expansion of the BCS will have a fair impact.

Of course, the concern with excipients in the context of biowaivers are, to the excipients, are they in fact not doing anything that's bad in terms of drug absorption or any other types of issues? And the things that come to mind are gastrointestinal transit, dissolution, stability, interacting with transporter metabolism, that sort

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of thing.

It would be very easy to point to certain things on here where there's very little studies. There's probably not much study with regard to excipients and transporters or excipients and metabolism. So in some ways these excipients, these common excipients, are very familiar, but in other ways they're actually very poorly studied.

So earlier this year, working with the FDA, we published this article -- this was back in January -- "Lack of in vivo impact of common excipients on oral drug absorption of BCS Class III drugs, cimetidine and acyclovir." So these were two model BCS Class III drugs.

They were subjected to two studies -- I'm going to very briefly describe them -- where the goal was to examine 14 common excipients. There was three capsule formulations for each drug cimetidine and acyclovir, where large quantities of excipients were in each of the various formulations.

Each drug was subjected to a fasted single-

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dose 4-way crossover study in healthy volunteers. There's an oral reference. And average BE was employed to assess impact of excipients. Here's the design of what I just talked about. And towards the bottom there, you can see there were three test capsules of cimetidine and three test capsules of acyclovir, each having large quantities of excipients collectively across 14 common excipients.

In study 2, there was follow-up with cimetidine, HPMC, and magnesium stearate. And the first study probably slowed down dissolution a little bit, with was not the interest. The interest was actually not so much a dissolution study but more looking at whether excipients have an impact on permeability or transit, that sort of thing.

So in study 2, HPMC and magnesium stearate were reduced. Okay? And then collectively across the series of studies, we were able to identify -- 12-of the excipients had no impact on bioavailability. And you can see, or maybe you

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can't, but in the second column after the listing of the excipient, you can see that very large quantities of these common excipients were studied.

The first two, microcrystalline cellulose and HPMC, actually failed Cmax, so we weren't able to say anything different than what's currently in the guidance with regard to qualitatively the same and quantitatively very similar. But overall, we think there was a lot of regulatory relief that could be found in this type of data.

So the conclusions were, 12 of the 14 were found to be non-problematic, and such that those excipients could be employed in Class III biowaivers such that they're not more than those that were studied here in this particular sequence of studies.

Again, HPMC and microcrystalline cellulose, because of the Cmax, with one particular formulation should be qualitatively the same and quantitatively very similar to the reference.

We do say in the paper some caveats. It's possible that other drugs might be different than

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these two particular ones, so there needs to be at least some level of caution. And then we also say the greatest concern would appear to be a drug that depends on an uptake transporter such that the excipient could possibly inhibit, by virtue of the excipient having the same molecular structure, similarity to the transporter's pharmacophore recognition site.

Then soon after that was published, there was actually -- some pharmacokineticist challenged the -- not so much the data, but just the interpretation. So this is where I'm going. There's probably a need to have some sort of a way forward to agree on what the biopharmaceutical implications of certain excipients are.

I think this is actually a quote from their letter. "Results obtained in our study should not be extrapolated to other drugs." They're suggesting that, oh, that's all great for those 2 drugs, acyclovir and cimetidine, but it shouldn't be extrapolated to any other Class III drugs. And then there's the reference there for our particular

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reply. And I do have to say, I think they raise a good point about just generalizability.

So to summarize, like many of the other speakers, I think there's a need for greater research in excipients. In some ways, they're very familiar but I think in other ways, in critical ways, they're actually -- there's a lack of data underpinning certain decisions that could be made that would benefit development.

There was also a presentation earlier today about pediatric applications. And as you know, that's a big area. There's been a lot of improvement in the last 10-years. There's perhaps been a doubling of labels, of drug labels. But I still think probably not much has been broadly generalized with regard to excipient use in children.

I recall some of the questions this morning about some of the excipient talks. And I guess one suggestion would be -- I'm thinking about some of the BCS biowaivers that are published in the Journal of Pharmaceutical Sciences, and those are

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extremely well-received. They're extremely highly referenced and downloaded.

Maybe the same sort of thing for the excipient side -- it would be very nice to have monographs of excipients with regard to at least biopharmaceutical aspects. A lot of chemistry aspects are well-known with regard to excipients, but with regard to some of these questions about ongoing drug quality, it's the biopharm side that seems to be a little less tied down. Thank you very much.

DR. LIONBERGER: Thanks very much.

Questions?

So is there a sense that the issue with excipients -- and you mentioned specifically -- is it really specifically interactions with transporters and enzymes? Or do we think there's other mechanisms by which they have biopharmaceutic effects?

DR. POLLI: My own personal opinion, I think that the most common excipients are used incredibly frequently, right, and in a variety of different

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formulations where there's a variety of different processing. And I think in -- for example, let's just take lactose. Lactose is used in very large quantities in many products.

But having said that, this opinion here, results should not be extrapolated to other drugs. One could put together an argument that the levels of lactose have not been well studied with regard to bioinequivalence and that sort of thing.

So it really is a matter of opinion, I think. There's not one source that summarizes, here's everything that we know about a particular excipient. Everyone probably knows the handbook, but that excipient handbook probably has nothing in it with regard to biopharmaceutic elements that often come into play. So I think a lot of things have to do with what paper you might be familiar with and how familiar are you with that particular excipient, that sort of thing.

DR. UHL: So your basic premise was that there's a need for more excipient research?

DR. POLLI: Yes. Well, maybe just a

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collating of what's already out there. And there's been a lot of right progress in the last year with regards to the inactive ingredient database. So maybe more of that sort of thing, what's already available.

What's the counter argument to someone saying, you can't generalize it to another drug? And you can go through the process that Dr. Lionberger was outlining in terms of, well, it could be this aspect. Could be transit. It could be some sort of metabolism concern. It could be some sort of transporter concern. But then you can ask the question -- I can tell you, there's not many articles that study excipient effects on metabolism.

So it's very easy to say there's not much you can hang your hat on. Having said that, these common excipients are used extensively. So it does come -- it often comes down to a matter of opinion ,I think.

DR. LIONBERGER: Thanks very much. Question? All right.

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So that concludes the formal program. Before I turn it over to Cook for closing remarks, I want to thank some of the people who did all the work to organize this meeting.

So that would especially be, if you were involved in the meeting at all, Thushi Amini and Jessica Alfaro, who are your contacts to set up the scheduling. Got the room. Got the logistics everywhere.

I know that Thushi's been responsible for this for the last four years and really been handing it off and training the apprentice. So I feel we just have to show up here and everything works. That's just a sign of excellence.

I also want to thank a lot of other staff from my office, Office of Research and Standards, especially Krista Andre, who has been working on the slides there, as well as all the staff from our office -- the scientists who are doing this were also the people who were checking you in. It's a great privilege to work here. I know that people in our office work very hard, willing to do

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anything it takes to get this meeting successful.

The work that I talked about this morning, there are people from our office involved with all of these external collaborations, making sure that they're running well, that they're meeting the needs of the generic drug program.

So there's a huge of amount of effort by a large number of staff that makes all of those activities that we're doing possible. And I just want to recognize them and thank them for all their efforts in making this meeting successful. So thank you very much.

(Applause.)

DR. LIONBERGER: So now our office director will make some closing remarks.

DR. UHL: Okay. So I get the dubious distinction of being the one that gets the last word in, although the words are given to me, thank you very much, by Thushi. So on behalf --

DR. LIONBERGER: She took off.

Closing Remarks

DR. UHL: That's okay. Needless to say, I

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have augmented and ad libbed a couple things here, so she's a little scared, I'm sure.

So on behalf of the FDA panel, I'd like to especially express my appreciation to the presenters today, and to everyone in the audience, whether you're attending in person or whether you are by webcast. And I don't think we have an exact number of how many are by webcast, but those of you out there, we're very appreciative of your interest in this topic and for your attention to the presentations discussed at today's meeting.

I'd also like to thank the panel members. Everybody sitting up here has more than enough work to do in their day job, and it's a Herculean feat, I think, to get -- what do we have up here -- 12 FDA leaders basically agreeing to sit here, listen to these presentations, engage with the presenters, and ask provocative questions so that Rob and his staff can work with all of the offices to create a very robust regulatory science program for GDUFA. So to all of you sitting up here, I thank you very much.

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I also want to echo some of Rob's thanks. I'd especially like to thank Jessica for all her hard work, and for making this public hearing run smoothly today. I want to thank Thushi for actually delegating and training Jessica.

So for those of you who have attended the last three years, Thushi usually has massive insomnia by this time, making sure that this meeting runs as smoothly as it does. And I have coached her extensively to delegate, so I am thrilled to see that she has. And Jessica, I thank you for letting her train you. So thank you very much.

I'd also like to thank all of Rob's staff. All of the staff in the Office of Research Standards at OGD are so engaged in this meeting and are -- really want to be sure that this runs smoothly. And I think, for those of you who are not with the agency, what Rob said is true. Our scientists are the ones out there greeting you.

This is not just standard admin support. I mean these are the workers behind the scene that provide you with what Rob showed, a pretty incredible return on investment of this program. If I was looking at my financial portfolio and saw a company with that kind of ROI, if I was allowed to invest in it, given the ethics standards here at the agency, I would wholeheartedly.

So to all of them, I thank them for making not just today run well, but for the success of this program. And I thank Rob for his leadership of this program.

Anyhow, for the Generic Drug Products, the GDUFA Regulatory Science Program is a platform that allows for collaboration between the FDA and our external stakeholders in order to develop generic drugs, and to find and establish new tools and methodologies that could be used in generic drug development and regulation.

As with our previous Part 15 hearings, this hearing was extremely productive and informative. FDA and OGD will carefully consider all the comments, both today physically at this meeting and as well from the submissions to the docket, as we

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develop the fiscal year 2017 regulatory science initiatives under GDUFA.

Once approved by the CDER center director, Dr. Janet Woodcock, the priorities list will be posted on the GDUFA regulatory science webpage. So it will be publicly available.

The docket will remain open until June 17th, so you have a little bit less than a month to still get any comments in. We strongly encourage all interested parties, so those attending in person, or those by webcast, or people that you know who may have an interest in this field who weren't able to attend, we ask you to please provide that information so that they can comment to the docket. It is your external input into this program that is making this program as robust as it is.

We also ask, from any of the presenters, if you have additional comments, if you can please as well send them to the docket, and ask you if you can elaborate on any of your recommendations. So I know there were questions posed that were different from what were in your slides, so please.

If anyone needs any further details about that, I ask that you please refer to the Federal Register Notice. Or, if you don't know where that is or how to find it, Jessica and Thushi can direct you to that.

So with that said, I thank everyone very much for your participation. I hope you have a nice, albeit rainy, weekend. And I would say that the final is that today's meeting is now concluded. So thank you.

(Applause.)

(Whereupon, at 4:15 p.m., the meeting was adjourned.)

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